MASTER IN NEURORREHABILITATION. Edition 2020-2021

Final Project of Master

Research Project Proposal

"Effect of Combined Anti-Nogo-A Antibodies and Intensive Rehabilitative Therapies on Acute Spinal Cord Injury: A Randomized Double-Blinded Placebo-Controlled Trial"

Valentin FOULQUIER

Tutored by Dr. Joan VIDAL SAMSÓ

Delivered the 06/06/2021

INDEX

Acknowledgments:

The establishment of this research project proposal could not have been possible without the help, availability and advices from:

VIDAL SAMSÓ Joan (PhD), Mentor and Teacher of the “Master en Neurorehabilitación” – Institut Guttmann – Universitary institute affiliated to the Universitat Autònoma de Barcelona (UAB)

All the teaching team from the “Master en Neurorehabilitación” – Institut Guttmann – Universitary institute affiliated to the Universitat Autònoma de Barcelona (UAB)

1 Abstract

Background: Recent investigation about the use of anti-Nogo to treat spinal cord injury (SCI) has been conducted on animals, and shown encouraging results concerning the enhancement of axonal sprouting, regrowth, and the neuroplasticity. Nowadays there is a need of translational research in order to apply the anti-Nogo antibody therapy on human subjects. (1) The inhibition of the CNS growth inhibitors after SCI such as the Nogo, appears to be a promising approach to enhance the neuroplasticity and neurite regrowth. Previous studies on animals have demonstrated encouraging results regarding the functionality recovery when applying specific Nogo inhibitors after SCI. Specific Nogo inhibitors refers to anti-Nogo antibodies ATI355 (human anti-Nogo antibody) described by Martin E. Schwab. Nowadays, the translational research regarding the appliance of ATI355 on human have begun and demonstrate – in despite of its limited evidence - that ATI355 was safe and well tolerated on human subject especially via bolus injection. Only Kucher et al. 2018 and the Nogo Inhibition in Spinal Cord Injury (NISCI) have conducted anti-Nogo intervention on human subjects until now. Moreover, the plasticity after an SCI can be exploited via rehabilitation. In fact, as the anti-Nogo therapy avoid the neuroplasticity collapse, it can be interesting to take advantage of it and use rehabilitation to recover as much lost function as possible. Thus, applying anti-Nogo therapy on human subject in addition to rehabilitative therapy that enhance neuroplasticity may give interesting results regarding the functionality recovery of the subject. The present study will focus on patients with acute traumatic SCI and take advantage of the changing and plastic environment related to the early physiopathology. **Objective:** The main objective of this study is to test if the anti-Nogo therapy can show an improvement of the motor and sensory function according to the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) of traumatic acute SCI patients, when combined with specific rehabilitative intervention. Then, secondary outcomes will be assessed to observe the functional improvement of patients through the change on grade of functional independence, functioning, upper limb function, gait and ambulation and quality of life; and the neurophysiological improvement will also be assessed through changes in nerve conducting velocity, somatosensory evoked potentials and motor evoked potentials. The assessment of the outcomes will be at different endpoints, at baseline, 3 months, and at 6-months and 1-year follow-up. **Methods:** In this monocentric randomized double-blinded placebo-controlled trial, two arms will be studied, an experimental group and a controlled group. Will be included in the study patients with acute nontraumatic SCI, level of injury at C4-T12 with AIS grade A-D and aged between 18 and 70 years old. In this study, the participant, the care provider, the investigator and the outcomes assessor will not know in which group will be the participants. The intervention will last for 3 months, it will consist on 6 ATI355 intrathecal bolus injections during 30 days for the experimental group, and a placebo of these ATI355 injections for the control group, and then, experimental and control group will both follow a specific intensive rehabilitation program for 90 days. **Discussion:** The ATI355 injection treatment is expected to be well tolerated by the participants and express a minimal number of adverse effects. The results obtained are expected to be above the minimal clinically studied values that will make the results become significant. Moreover, the values obtained in the experimental group are expected to be better than the one of the control group. And the results registered at the different endpoints are hoped to be better along the time progression. Thus, the final results obtained at the end of the study are expected to confirm the alternative hypothesis.

2 Introduction

2.1 Spinal Cord Injury

2.1.1 Definition

The spinal cord can be injured along the lifetime of an individual, then we speak about a Spinal Cord Injury. The spinal cord injury (SCI) is defined by the World Health organization (WHO) as a "damage to the spinal cord resulting from trauma or from disease or degeneration". In fact, different mechanisms of injury and causes may induce this trauma, and its treatment represent a real challenge among the neuroscience society.

2.1.2 Epidemiology and aetiology of the injury

In 2016, there was in the world a global incidence close to 0.93 million (0.78 – 1.16 million) and a global prevalence of 27 million (25-30 million) of SCI. SCI have been shown to occurs in men more than women, between the age 20 and 40 years old, and they occur more at neck level or above than under the neck level. The leading cause of SCI appears to be falls in most of the countries, but in North and middle east Africa conflict and terrorism is the leading cause of SCI by far. Also, the transport injuries and motor vehicle road injuries are common in many countries. (2)

2.1.3 Physiopathology of the spinal cord injury

The pathophysiology of the SCI can be explain dividing it into two main phases, the primary injury and the secondary injury. The primary phase corresponds to the mechanical injury where fractures or/and dislocations of the spinal column occurs, with a possible rupture of axons, blood vessels and cell membrane. And the secondary injury refers to the dysfunctions resulting from the vascular system, the presence of edema, inflammation, delayed apoptosis of cells and excitotoxicity. The secondary phase is much more complex, it extends on a larger period and induces the tissue destruction even after the neurological deficit appearance. The second phase is divided into four sub-phases, the *immediate*, the *acute*, the *intermediate* and the *chronic* one - see figure 1. The Figure 1 resume the SCI pathophysiology. (3)

During the early acute phase occurs the continuing phenomenon of haemorrhaging, edema increasing size and inflammation, but also new phenomenon appears, the ionic dysregulation, a free radical production, the glutamate-mediated excitotoxicity, and an immune-associated neurotoxicity. All those phenomena conduct to cell death and larger axonal injury. The disruption of vascular structure, the haemorrhaging and the ischemia that result from it are the key components of this secondary injury as they affect the neurons and glia.

The subacute phase is the one during which the cell-based therapeutic strategies are more prone to be applied. During this phase the astroglial or astrocytic scar is formed by an increased astrocytic activity linked with the filament glial fibrillary acidic protein. This scar permits the axonal regeneration playing the role of physical and chemical barrier protection. The astrocytes will also play the role of re-establishing the ionic homeostasis and the blood brain barrier (BBB) integrity, to solve the edema and limit the immune cells infiltration.

To resume, the astrocytic response serves to restore and maintain the BBB, re-establish the homeostasis at ionic level and avoid the infiltration of cytotoxic immune cells while the formation of the astrocytic scar. But the astrocytic scar also diminish the axons regrowth and limit the recovery of functional capacities. (3–6)

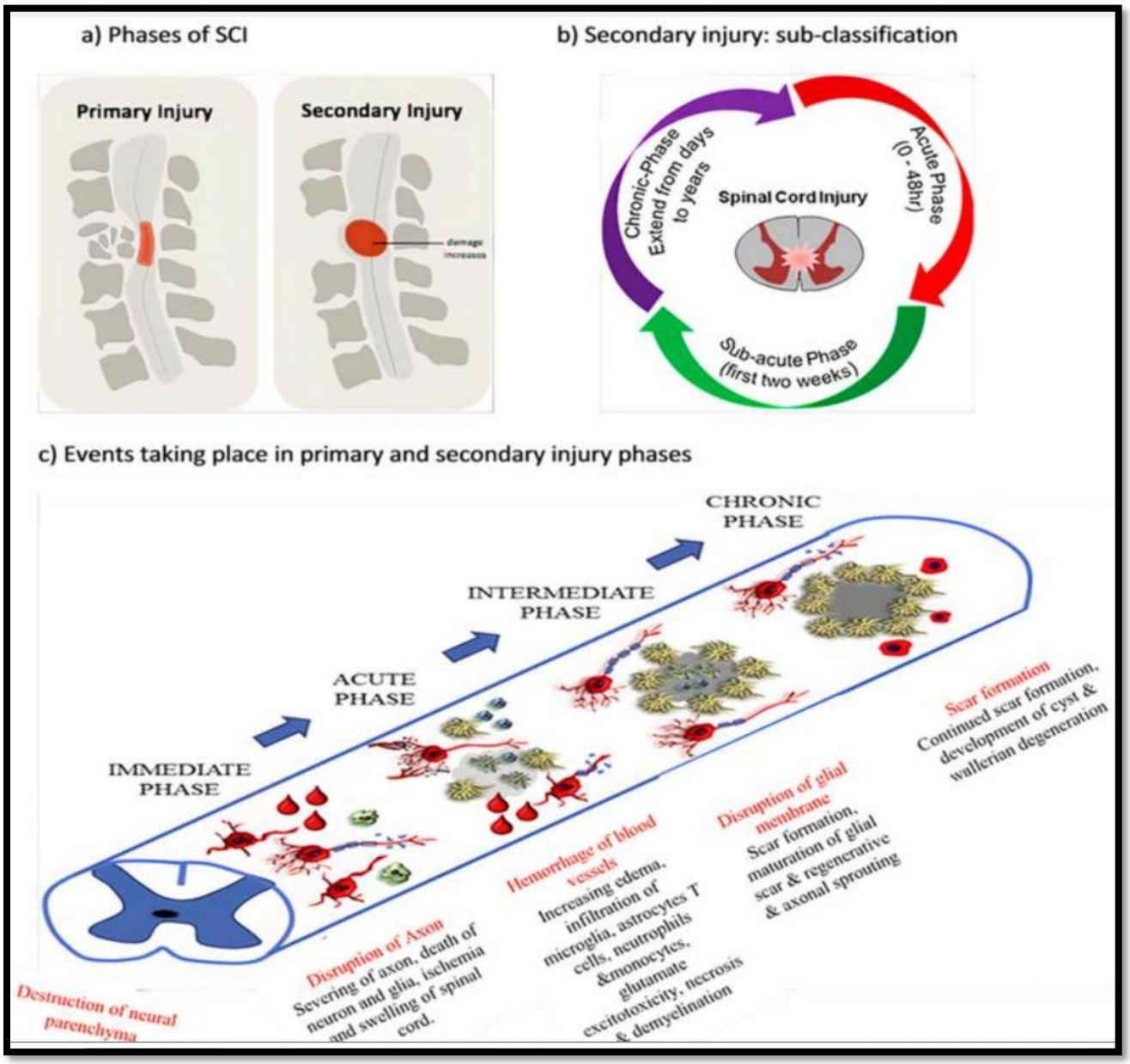


Figure 1: Pathophysiology of SCI. a) Phases of SCI, b) The sub-classification of the secondary injury, c) Different events taking place during the injury phases. Scheme from Anjum A. et al. 2020, International Journal of Molecular Sciences.

2.2 Plasticity and Regeneration

The brain is an organ that possess the capacity to change all along the lifetime. From its birth until his death the human being will be exposed to stimuli through experiences that will reorganize his brain's connections. We call this mechanism "activity-dependent" where the brain's reorganization depends on the activity applied on it. Whereby the study of brain and most generally of all central nervous system will be considered as studying a structure in constant evolution. During all the evolution's time, the transformation of many elements such as, not only the formation of connections, but also the gene expression, the growth of neurons, and the alteration of synaptic efficacy will be part of the brain's changes. (7)

Even considering that this reorganization has its limitation among patients deeply injured, the concept of "functional reorganization" and "activity-dependent" mechanism will constitute the key elements of the plasticity on which we will rely to reach the functional improvement of the injured individual – see figure 2.

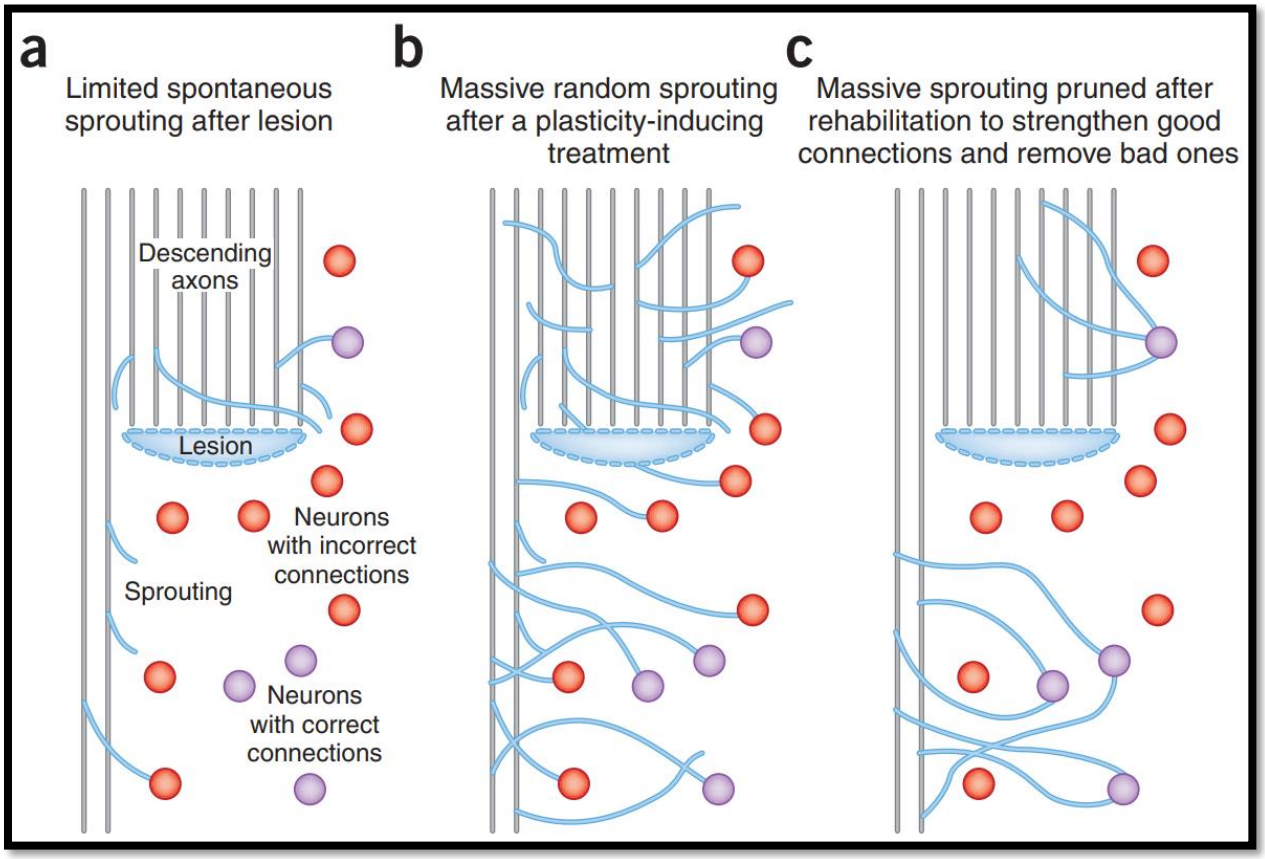


Figure 2: Formation of new connections through sprouting from injured and uninjured axons. Scheme from J.W. Fawcett et al., Nat Med. 2009;15(7):735–6.

In our case the plasticity term refers to the sprouting and growth of axons that permits to rewire the CNS. The connection's plasticity at the spinal cord level permit also a certain capacity of adaptation to

the injury, for that reason it represents a great advantage at the time of therapy intervention. Following a SCI, plasticity can be inhibited through specific inhibitors such as myelin-associated inhibitors and matrix molecules. (8,9)

The regeneration of the CNS following an injury is considerably lower in comparison with the peripheral nervous system (PNS). It is responsible of a poor prognosis of functional recovery. The CNS can be injured in many ways, such as direct physical trauma, lack of oxygen, neurodegenerative diseases, but in the most severe cases the regeneration of injured axons is difficult to enhance.

2.3 Different strategies for SCI treatment

The treatment of the SCI represents a real challenge among the neuroscientist and practicians specialized on this field. Along the times different strategies have been investigated to treat SCI. Medication, surgery, rehabilitation, and some advanced therapies are included in the investigation field of treatment against SCI. Until now, no consensual approach has been standardized, but the evidence shows each time a progression in the development of a treatment. (4) That's why the term of "strategy" seems more adapted than the one of "treatment" to describe this progressive improvement.

2.3.1.1 Surgery

Most of the time a SCI is accompanied by a fracture and a contusion of the vertebral column that can narrow the vertebral canal. The greatest challenge concerning the surgery approach, is about the controversial issues following the timing. For sure the essential objective of the surgery is to relieve the lesion by decompression, fracture healing and stabilization of the zone. Some studies reported better biological and neurological outcomes with an early surgical decompression. While other studies shown similar effect of an early surgical decompression and a delayed one. However, the early decompression surgery is thought to be a better option, especially in patients with deteriorating neurology. Even if no precise and optimal timing have been yet clearly stated as superiorly efficient, the practicians recommend a decompression surgical intervention within the 24 hours post-injury. The Surgical Treatment for Acute Spinal Cord Injury Study (STASCIS) trial, is a study evaluating the impact that can have the early surgical decompression and its timing on the SCI treatment. (4,5) However, this field represent a major source of investigation and need further research to be more precisely understood.

2.3.1.2 Medication

The pharmaceutical treatment also represents a branch of the SCI therapeutic approach. Different treatments were experimented considering the pathophysiological mechanism of the SCI.

- First, the Steroids (corticosteroids) use was popular during many years due to their anti-inflammatory action. They may act on the modulation of the inflammation and immune response. Despite the lack of understanding on their neuroprotective effect, they were more used to reduce the edema size in acute phase of SCI. (4)
- The Methylprednisolone is defined as a synthetic glucocorticoid that has been used for SCI edema treatment for a long time. Nowadays the use of methylprednisolone is influenced by the National Acute Spinal Cord Injury Studies (NASCIS) I, II and III. And following those studies, the use of methylprednisolone has been more criticized, and its application stay questionable. Minimal effectiveness in neurological outcomes has been found and, in some cases, worsen effects were reported such as increase of infection rate and secondary death.
- The glycosphingolipids Ganglioside GM-1 may influence the restoration of neuronal and neuroprotective function. They show significative and encouraging results on neural fibres outgrowth, increasing plasticity, apoptosis prevention and excitotoxicity inhibition. Positive effects were reported only in patients with incomplete SCI (patients with AIS B-E) and no effects were obtained on patients with complete SCI (patients with AIS A) - see annex 1.
- Many others medications or techniques has been experimented along the years, we can cite the thyrotropin releasing hormone, nimodipine, gacyclidine (GK11), magnesium, hypothermia application, minocycline, cethrin, erythropoietin, estrogen, progesterone, cyclooxygenase inhibitors, riluzole, atorvastatin and antioxidants; but none of them have been standardized and commonly reported as more efficient against SCI. (4)

2.3.1.3 Rehabilitation

The rehabilitation process represents the keystone of the SCI treatment, it permits to optimize the recovery of neurological function. The beneficial effects of the rehabilitation or also called neurorehabilitation are the pain management, the prevention of complication resulting from the lesion and training the neural circuits. In despite of the presence of endogenous inhibitors in the injured CNS that limits the new connections formations, the rehabilitation is thought to improve the CNS plasticity and stronger the specific sensorimotor pathways that permit a greater stability of the neuronal network. Following the studies that have investigated this field, the rehabilitation may have a stronger effect when coupled with others strategies such as medication or regenerative therapies. (3,8)

The neurorehabilitation is conducted by a multidisciplinary team, including physiotherapists, that performs specific techniques to optimize and gain the maximum amount of functionality.

The locomotion pattern rehabilitation is one of the best clinical intervention that can be conducted on patient with SCI. In fact, this pattern is trained with the objective of activating both upper and lower neurological levels from the injury site and enhance the CNS plasticity. Activating spared neural fibres and circuitry is hoped to permit new connections responsible for the functionality recovery. To favour this pattern of locomotion, functional electrical stimulation (FES) and training with weight-assisted treadmill appears like great options. These therapies have the common goal to elicit a locomotor circuit located inside the spinal cord called central pattern generators (CPG) that may stimulate the neural networks below the lesion level and restore the movements of the limbs. (3,6)

In other hand, the activity of neural fibres may be promoted by the appliance of partial-weight supported walking (PWSW), electrical stimulation on stationary bicycle, passive limb movements and tendon transfers. (8)

The advantage of active neurorehabilitation is the muscle mass increase which helps to maintain the skin integrity and the bone density, that subsequently prevent the fractures, the formation of blood clots and reduce the spasticity and eventually promote regeneration. Thus, the rehabilitation will be oriented onto improving the voluntary as well as the involuntary functions of motor control to optimize the functional recovery. For sure, the rehabilitation needs to be coupled with other therapies to be effective and does not constitute a cure when applied alone. Some combinational approach has been studied as they represent actually the best hope in the race of finding SCI therapy. (3,6)

2.4 Anti-Nogo strategy

Many components were found from the membrane, the extracellular matrix of nervous cells, possessing a strong inhibitory action on neural fibres, such as secretory proteins or glycoproteins. Those specific components were localized in the CNS white matter, but also in myelin and in the scar's lesion. (5) The following paragraph will focus on one of those cellular components, the Nogo and its possible implication in therapeutic strategies.

The CNS myelin possess two inhibitory fractions called NI-35 and NI-250. The fraction NI-250 have been renamed Nogo-A and form part of the reticulon (RTN) family as it is encoded by the rtn4 gene as well as the Nogo-B and Nogo-C. The precise region of the Nogo that induce the inhibition of the neurite growth is the Nogo-66 which is a loop-region composed of a 66-amino acid sequence located between the two hydrophobics regions. Then the Nogo-66 enhance the neurite growth inhibition by binding with a plasma membrane receptor called NgR (glycosylphosphatidylinositol receptor) – see figure 4. The Nogo-A is located in the tubular endoplasmic reticulum on the cell surface of the oligodendrocytes and it apply it action on the oligodendrocyte's myelin, but also on the neurons of the hippocampus and the cortex where the plasticity is highly present. (10,11)

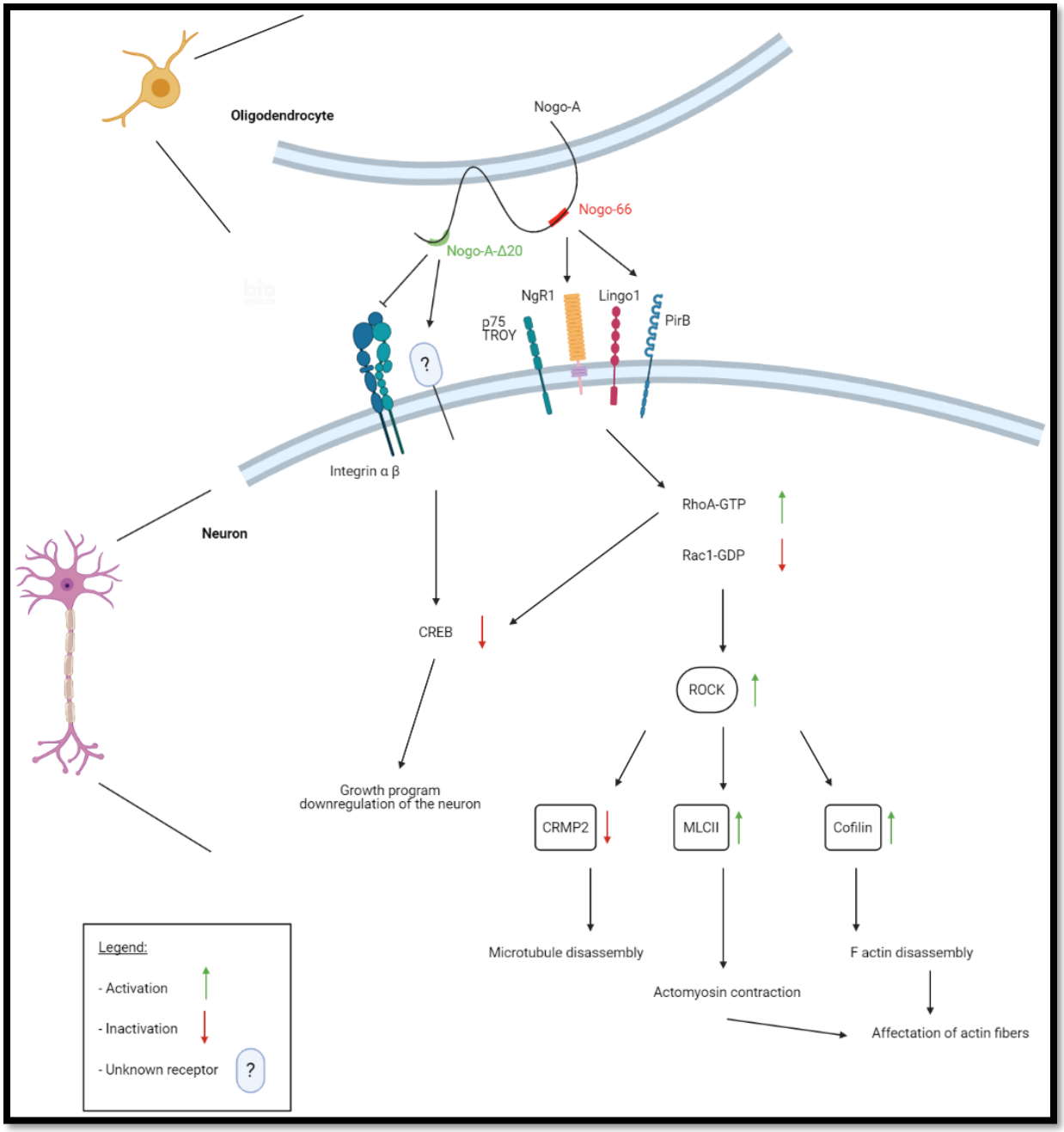


Figure 4: The following scheme illustrate the physiology of the inhibition mechanism of the neurite growth or outgrowth.

Nogo-A neutralizing antibodies treatment also called anti-Nogo therapy has shown to increase the neuronal growth and outgrowth, and regenerative sprouting when applied in acute phases of an injured CNS, like patients with SCI. And similar effects were observed by blocking the NgR1 receptor and LINGO1 protein.

Also, after a CNS injury, a compensatory sprouting of spared fibres like in non-regenerative plasticity has been proven to be elicited by deletion of the Nogo-A. Which appears to be an interesting discovery for the future, because it means that this non-regenerative plasticity of uninjured fibres may permit to

create parallel (or so called “detour”) connections by going through the injured and denervated area and so re-innervated the spinal cord. Thus, the real goal of the anti-Nogo therapy should not be the axon regrowth, but the plasticity sprouting of uninjured axons. In conclusion, it may be possible to improve the SCI treatment, increasing the few presence of plasticity and enhancing the intact circuit reorganization on the injury site by blocking the Nogo-A signalling pathway and offer a favourable environment to the preserved axons. (10–12)

From the discovery of these proteins inhibitory fractions called NI-35 and NI-250, it became possible to develop a monoclonal antibody called IN-1 that permit the inhibition of the inhibitory properties of these fractions. The “in vivo” investigation of the IN-1 gave promising results, until obtaining improvements in functionality on the individuals tested. Following those experiments, the development of an intrathecal application of anti-Nogo A antibody became possible and permit to establish the first anti-Nogo therapy trials. More precisely, the immunoglobulin G (IgG) called ATI355 has been shown to have an inhibitory action on the Nogo protein – see figure 5. (13,14)

The anti-Nogo antibodies are avoiding the Nogo-A to reach the receptors on the neuron’s membrane and thus avoid its inhibitory effect on the neurite regrowth. The anti-Nogo antibody IN-1 target the inhibitors NI-250 and NI-35 and inactivate the Nogo – see figure 5. And after several trials it was observed an inhibition of the Nogo-66 that was inducing a regrowth of injured axons and an increased activity of sprouting on patients with SCI. (3,10)

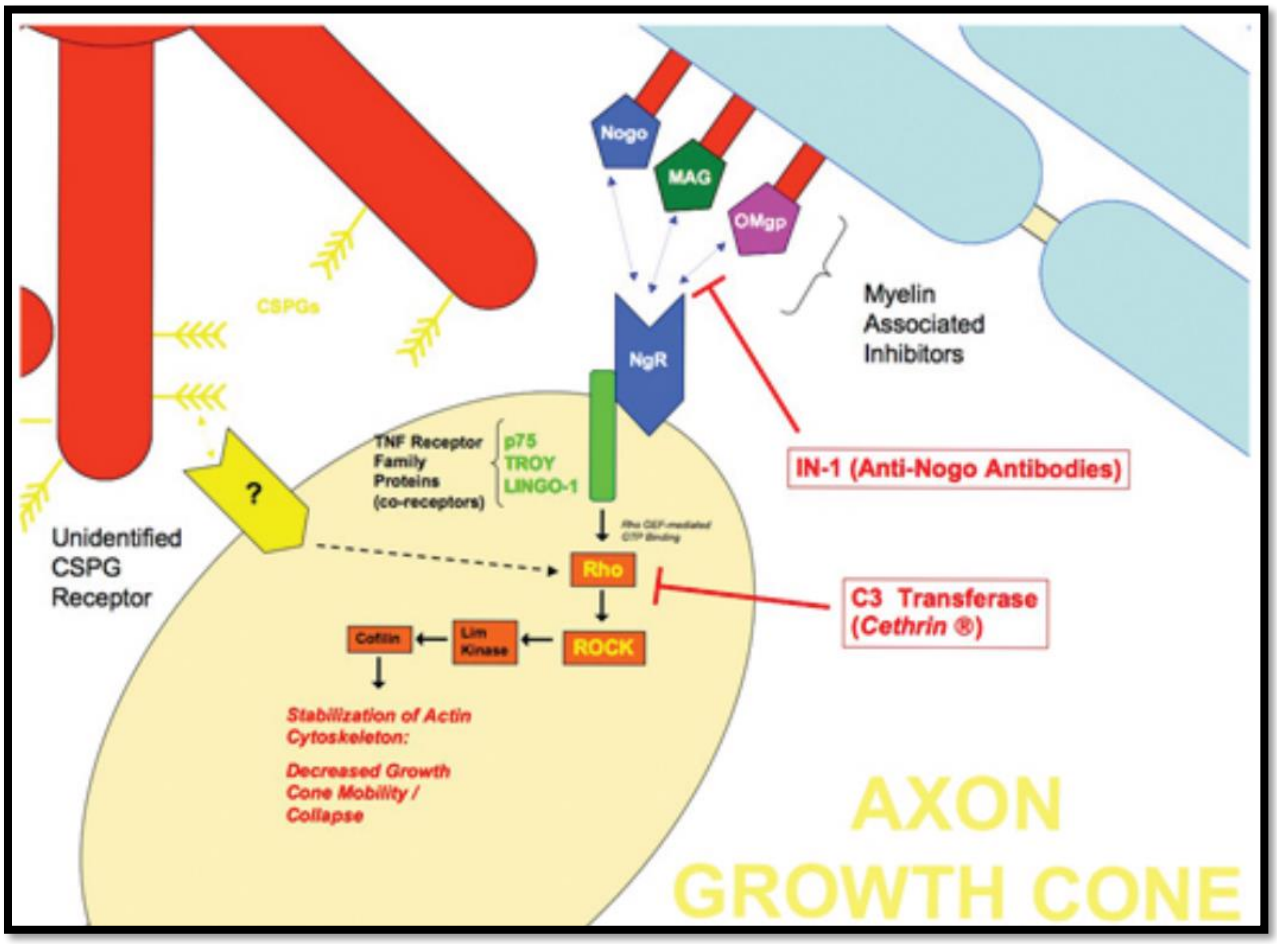


Figure 5: Scheme of the glial inhibition during the axonal growth after a SCI. Scheme from J.W. Rowland et al., Neurosurg Focus 25 (5):E2, 2008.

2.4.1 Functional impact of different strategies and their combination

The different strategies applied to treat SCI have as common objective to restore and improve the functionality capacities of the individual treated. A translational approach permits to observe on a more general way the treatment applied on individual with SCI. The general goal is to see what the clinical findings regarding the application of the anti-Nogo therapy in clinical application were.

2.4.2 Functional recovery

The anti-Nogo therapy appears to enhance the recovery of the following functions: the locomotion, the climbing or even the fingers dexterity in rats experiments. (14)

Karim et al. 2001 (15) explained in their review the mechanism of functional recovery related to anti-Nogo antibodies therapy. In fact, it was shown some mechanism of functional recovery involving adaptations and the plasticity re-arrangement of spared fibres below the injury level. Among these mechanisms we found some compensatory ones at the upper and lower limbs levels, that permitted the grasping and walking functions. But also, the CPG related to an activity-dependent adaptation that can be elicited after training. This CPG experiment shown activation of the lower limbs that permitted a basic gait pattern through stepping and weight bearing in cats.

In despite of this promising results obtained through *in vitro* and *in vivo* investigation, the anti-Nogo therapy appears to be difficult to be applied clinically. In fact, the lack of an appropriate procedure for administration of anti-Nogo A antibodies seems to compromise its application in daily practice. However, it is suggested that the optimization of the functional recovery following a SCI can be made via a combination of different advanced therapies, such as stem cells or Schwann cell transplant, and olfactory ensheathing glia – see figure 6. (15)

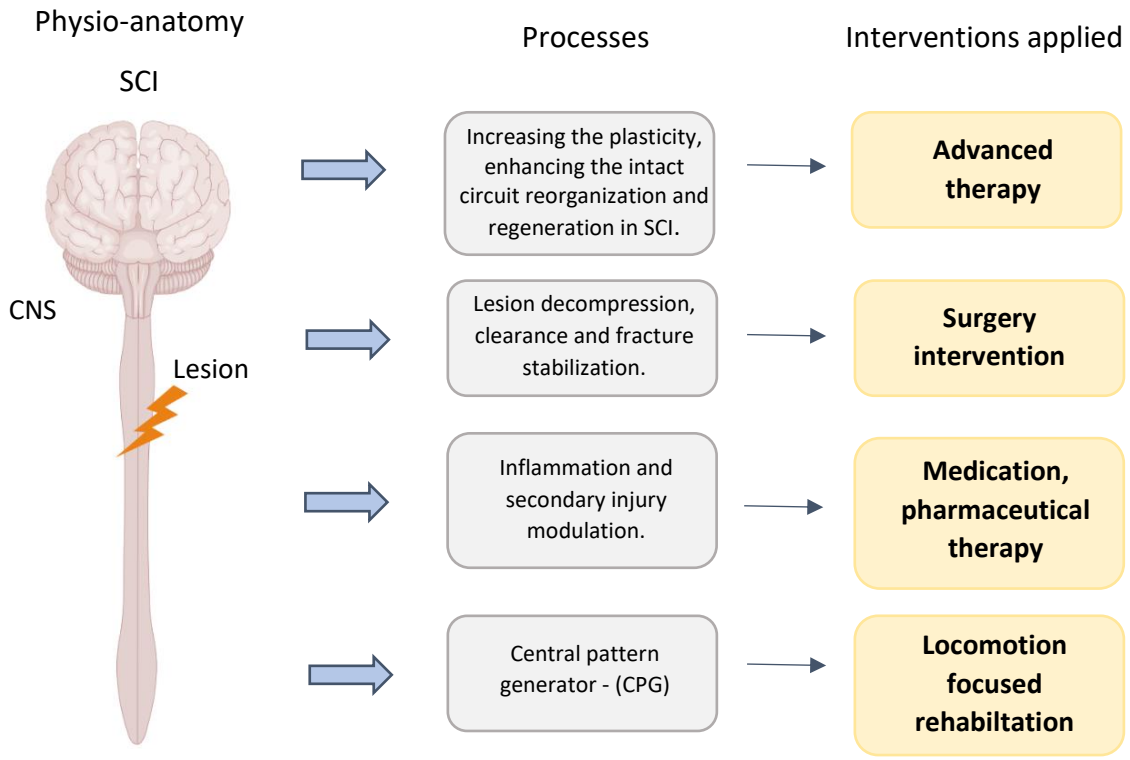


Figure 6: The following scheme demonstrated the different therapeutic strategies that permits to treat a spinal cord injury.

2.4.3 Combination of therapeutic strategies

Few of the strategies previously studied seems to represent a curative treatment for SCI. In fact, the translational application of these strategies showed some issues of timing and funding. They are cost effective, time-consuming studies that ask for many devices and qualified practicians. However, those therapies have shown encouraging and promising results concerning small but significative neurological improvement. As suggest the study of Karim et al. 2001 (15), the combination of different advanced therapies may permit to optimize this neurological recovery and then improve the functional recovery. (5,14) But adopting a more global vision on the therapeutic approach of SCI may allow us to suggest the combination of all these strategies to optimize functional recovery. In fact, combining advanced therapy with surgical treatment and rehabilitation may provide better results than only advanced therapy application. In all case, the nervous system plasticity is activity-dependent, which mean that no treatment based only on nervous fibres regeneration or regrowth, medication administration or surgery can optimize the functional recovery. Indeed, these treatments will permit a more permissive environment in order to allow the plastic changes to occur, while the rehabilitative treatment will permit the recovery of function via plastic-rearrangement. (8)

To conclude, no “miracle treatment” exist to treat SCI, but over the times, significative improvement got closer from a combination treatment where the rehabilitation represents the keystone of it – see figure 7.

Nowadays and for the future, trials on combinations of different treatments and the doses applied should be investigated to reach a consensus regarding treatment of SCI.

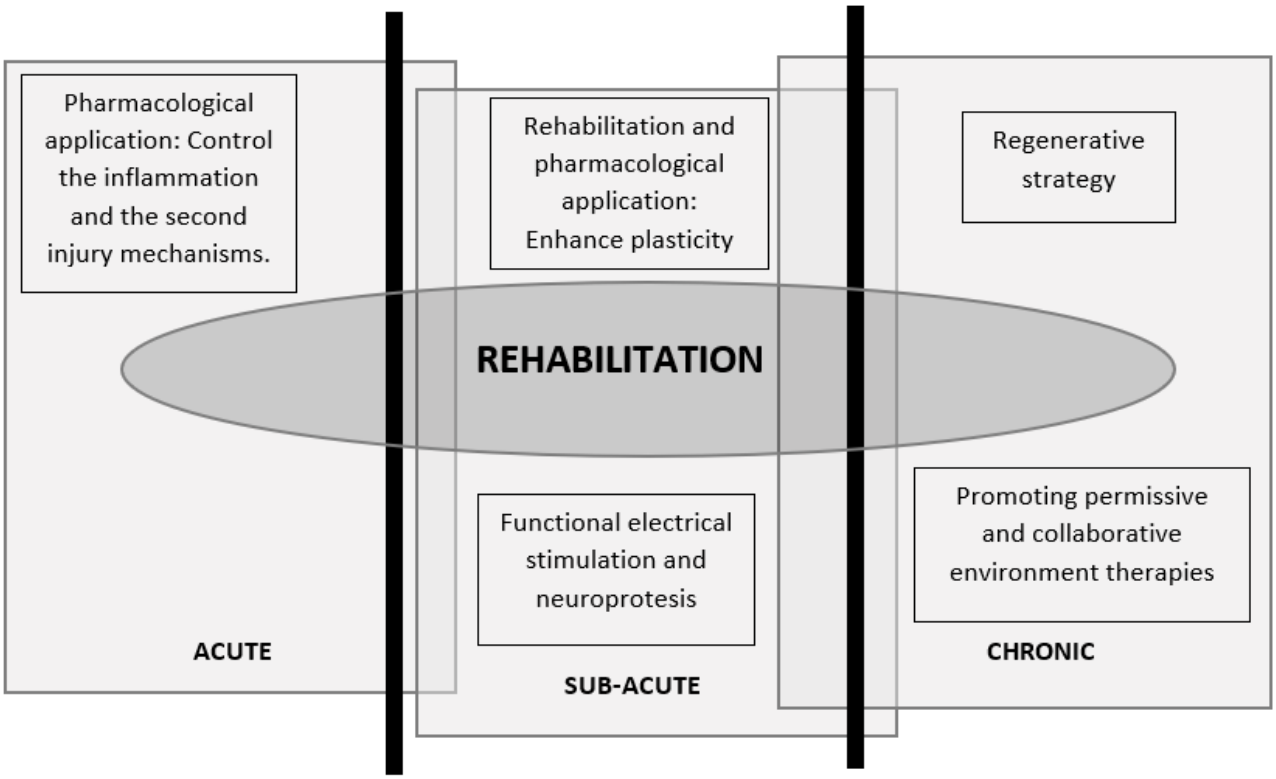


Figure 7: Convergent therapeutic strategies needed to restore the functionality after a SCI at different stages of the injury.

3 Objectives

3.1 Primary objectives

The main objective of this study is to test if the anti-Nogo therapy can show an improvement of the motor and sensory function according to the International Standards for the Neurological Classification of Spinal Cord Injury of traumatic acute SCI patients, when combined with specific rehabilitative intervention.

3.2 Secondary objectives

The secondary objectives will be to observe:

- Change on grade of functional independence, evaluated by the Functional Independence Measure and Functional Assessment Measure (FIM+FAM)
- Change on functioning, evaluated by the Spinal Cord Independence Measure (SCIM-III)
- Change on upper limb function, evaluated by the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP)
- Change on the Walking Index for Spinal Cord Injury (WISCI) measurement
- Change on 10-meter walk test (10mWT) measurements
- Change on 6-minute walking test (6MWT) measurements
- Change on quality of life (SF36)
- Change on nerve conducting velocity
- Change on somatosensory evoked potentials
- Change on motor evoked potentials

4 Hypothesis

Null hypothesis: The patients with acute traumatic spinal cord injury do not show a major neurological improvement of the motor and sensory function according to the International Standards for the Neurological Classification of Spinal Cord Injury while the anti-Nogo therapy is combined with specific rehabilitative intervention.

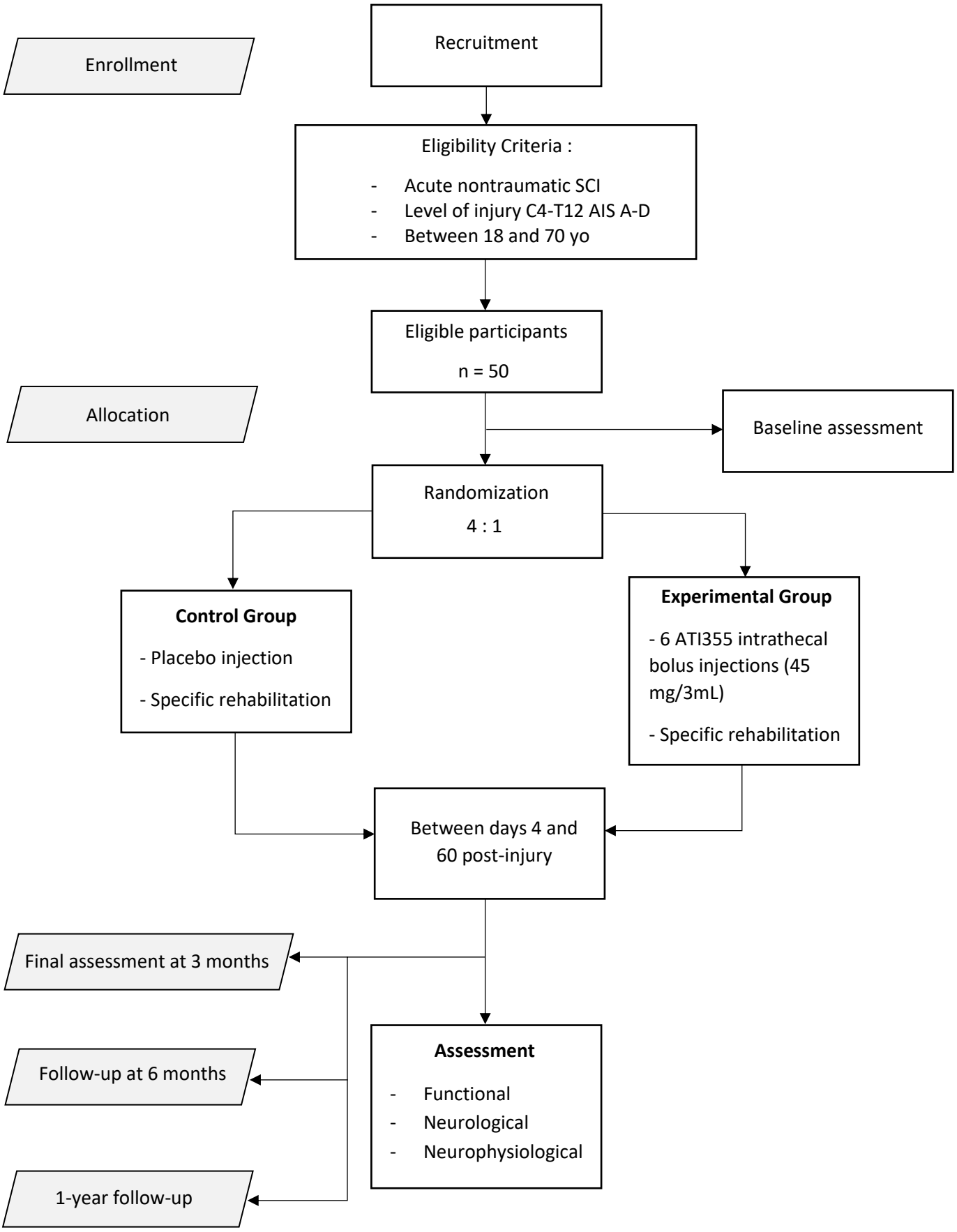
Alternative hypothesis: The patients with acute traumatic spinal cord injury show a major neurological improvement of the motor and sensory function according to the International Standards for the Neurological Classification of Spinal Cord Injury while the anti-Nogo therapy is combined with specific rehabilitative intervention.

5 Methods

5.1 Study Design

This study will be conducted as a monocentric randomized double-blinded controlled trial, where two arms will be studied, an experimental group and a controlled group. The intervention (anti-Nogo antibody) will be applied on the experimental group and a placebo will be applied on the control group.

5.2 Flow Diagram of the study



5.3 Study setting and Recruitment

This study will be conducted as a monocentric study in the Institut Guttmann (Badalona, Spain). The resources used along the study will be owned by this centre. The study will last for 3 months with a 6 months and a 1-year follow-up, as the majority of the recovery in SCI patients occurs during the first 3 months even if it has been observed some considerable but rare improvement until the 18 months. (13,16,17)

The recruitment of the participant will be held by the investigators in charge of the study. The method of recruitment will consist on personal asking to the patients that attend to the centre. Once the study will be explained to the patients and the investigator in charge will be sure that the patients understand the stakes that represent this study, then the patient will read and sign the informed consent. Afterward, the patient will follow a consultation of eligibility with a medical doctor, and he/she will be incorporated in the study.

5.4 Sample size

The sample size calculation has been made by inspiring from the previous studies conducting patients with SCI and based on the results of the review from Fawcett JW et al. 2006. (16)

The sample size will be of 50 patients distributed with a ratio of 4:1, where there will be 40 patients in the experimental group and 10 patients in the control group. (1,13,18)

5.5 Eligibility Criteria

Inclusion criteria	**Exclusion criteria**
• Acute traumatic spinal cord injury with neurological level of injury C1-T12 with AIS classification A-D	• Chronic spinal cord injury
• Recruitment at 4-90 days post-injury	• Nontraumatic para- or tetraplegia
• Personal motivation to achieve and complete the different phases of the study	• Complete anatomical spinal cord transection confirmed by magnetic resonance imaging
• Patient able to understand the challenges and the possible consequences of the study	• Aetiology of ballistic injury related to a direct penetration in spinal cords such as knife and gunshot injuries
• Between 18 and 70 years old	• MRI indicating complete obstruction of the intrathecal space
• Patients clinically and hemodynamically stables at baseline	• Patients requiring additional surgery to stabilize the spine during administration of ATI355

• No dependence to mechanical ventilation	• Important damage in lumbar and brachial plexus
• Patient signed and understand the written informed consent	• Injuries that are considered, by the investigator, to interfere in the assessment of the spinal cord function, including severe head trauma
	• Presence of severe systemic disease involving lung, liver, gastrointestinal, cardiac, immunodeficiency or kidney disease; or active malignancy
	• History of an acute episode of Guillain-Barre syndrome
	• History of recent (6 months) meningitis or meningoencephalitis
	• History of refractory epilepsy
	• History of or current autoimmune disease
	• Patients with uncontrolled bleeding diathesis and/or that need concomitant treatment with coumarin anticoagulant
	• Patient with haemoglobin levels below <8.0 g/dL
	• Patients who required greater than >10 blood transfusions required since SCI
	• Presence of any kind of unstable medical or psychiatric condition
	• Pregnant or nursing women
	• Unconscious patients
	• History of immune mediated reaction or life-threatening allergic
	• History of hypersensitivity to the investigational medicinal product (ATI355) or to any drug with similar chemical structure (determined by allergy skin test)
	• Participating in any clinical investigation within 4 weeks prior to dosing
	• Patients with infection around the site of intrathecal injections application
	• Presence of cauda equina damage confirmed by nerve conduction velocity
	• Drug dependence during the 6 months preceding the study

	• Patients unable to communicate effectively with the neurological examiner such that data validity could be compromised

5.6 Randomization

The random allocation of participants in both intervention and control group will follow a ratio of 4:1 and will be held by one investigator. The investigator will use the computer software "SPSS Statistics IBM".

5.7 Blinding

The present study will be presented as a double-blinded study, where the participant, the care provider, the investigator and the outcomes assessor will not know to which group belongs the subject receiving the intervention.

5.8 Intervention Control/Experimental groups

The intervention will be applied on a specific population that will nevertheless try to represent as much as possible a great number of persons in the same situation. Patient with different degrees of complete and incomplete spinal cord injuries will be targeted. The enrolment of tetraplegic and paraplegic patients with different degrees of injury is essential, as it will permit to evaluate the limits and the diversity of results that are possible to obtain with the intervention.

5.8.1 Control group

The intervention applied on the control group will consist on an intensive specific therapy and placebo injections of ATI355. The intensive specific therapy will be defined by first, an early rehabilitation once the patient will be considered stable, the intervention can be applied from the fourth day post-injury. The aim of this early rehabilitation will be the prevention of possible complications. This early intervention will consist on passive range of motion (ROM) exercises, patient positioning every 2-3 hours in order to protect fragile and exposed structures (organs and joints), stretching, limbs mobilizations, breathing exercises, and an important family or relative inclusion and participation to the treatment. (19) Then, the patients will undergo a functional rehabilitation composed of strength training, cardiovascular-focused exercise, respiratory conditioning, transfer or mobility training, stretching to prevent muscle contractures, weight-supported locomotor training and robotic therapies (Armeo, Eksoskeleton). (20) More specifically this intensive specific therapy will be conducted for the whole study period until the final assessment. Whiteneck G. et al with the SCIRehab project reported

that, the physiotherapy and occupational therapy rehabilitation represent around 60% of the whole therapy time, and the minimal time required for patients during a rehabilitation process is about 3 hours per day during 5 days a week, with an average considered around 24 hours per week during 5 days a week. (21) In our case an increase of these values will be applied to reach 5 hours per day during 5 days a week of general rehabilitation, as an intensive approach is needed. The intensive therapy will last for 90 days (3months) and will be provided by multidisciplinary team of care providers (physiotherapist, occupational therapist, sport therapist, nurse, psychiatrists).

The placebo injections will replace the ATI355 injection and will be administered at specific endpoints by the care providers (physicians).

For all patients the adherence to the placebo and rehabilitation intervention will be monitored and any missed session or injection will be reported in a unipersonal calendar with its specific cause (see annex 2).

5.8.2 Experimental group

The experimental group will follow the same intensive specific rehabilitation therapy than the control group, following the same timelines and will be treated, assessed and investigated by the same peoples as for the control group.

However, this group will receive real ATI355 injections rather than placebo one. For ethical reasons, in the whole study sample (n = 50), there will be four time more receivers of real ATI355 than placebo injections. The patients will receive 6 intrathecal bolus injections with a dose of 45 mg/3mL of ATI355 for 30 days. The placebo injections timeline will fit with the one of real ATI355 injection. The participants will receive the first injection from first week after their incorporation in the study.

The administration protocol will follow the same guidelines as the one of the previous studies made on human. Moreover, it has been reported that intermittent intrathecal bolus injection of ATI355 was safer and better tolerated by participants. (1,13)

As with the control group, the adherence to treatment will be monitored and reported, and any missed session will be registered in a unipersonal calendar (see annex 2). Any patients that were not continuing the ATI355 treatment were requested to attend all the assessments.

5.9 Outcomes

All the tests, scales and proof will be realized by trained specialists (medical doctor, physiotherapist or occupational therapist), and if the assessment has been realized in any special condition (prothesis, help from pair, state of fatigue…), then it will be recorded on the evaluation sheet by the executor.

5.9.1 Neurological improvement

Motor and sensory function improvement

The neurological improvement constitutes the main outcome of the study. At the moment they join the study (at baseline), patients will be neurologically assessed by a medical doctor using the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI). The ISNCSCI is a specific neurological classification tool designed by the American Spinal Injury Association (ASIA) used at level of investigation to quantify a neurological impairment after a SCI (see annex 3). (22) During this evaluation the sensory and motor score of each patient will be registered and the same process will be repeated at all end points, 3 months final assessment, 6 months and 1-year follow-up. The pin-prick and light touch sensation will be evaluated in both right and left body sides following the 28 dermatomes, and the muscle strength will be assessed through the contraction of 10 key muscles (5 at C5-T1 level and 5 at L2-S1 level) on each body sides. Once the results will be obtained a triple comparison will be made, one between both groups (control and experimental), another one between the different endpoints assessment results and a last one between the scores obtained by each patient and the normal improvement due to spontaneous recovery after SCI.

5.9.2 Functional improvement

The different results of functional improvement obtained along the study may not be compared to hoped standard values of spontaneous recovery – as previously in the neurological improvement outcomes – but they will be compared between themselves at the different endpoints and between both control and experimental groups.

5.9.2.1 Functional independence

Considering the intervention applied on patients, a functional independence improvement is hoped. Then a way to assess this outcome will be via the coupled Functional Independence Measure and Functional Assessment Measure (FIM+FAM) (see annex 4). These scales contain 30 items that permits to assess the level of independence of the participants, the amount of assistance they need and the eventual use of assistive devices. These scale can be administered rapidly with minimal material (pen and paper). (23) The scores will be calculated at all timepoint and changes in grade will be interpreted in both groups.

5.9.2.2 Daily functioning

To assess the daily functioning or activity of daily living (ADL) the SCIM-III (see annex 5) will be used as it is a scale specifically developed for SCI patients with good specificity. In fact, this scale represents a

frequently used tool in research as it requires no specific equipment and a performance time around 30-45 minutes. Then the 19 items of the scale will be filled by one or several researchers within a period of 72 hours. (24)

5.9.2.3 Upper limb function

The upper limb function will be assessed specifically among the tetraplegic participants with all AIS grades as the paraplegic participants are - by definition - in possession of their full hand functions. The upper limb functions will be assessed through a specific scale called the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) that possess a good test-retest validity and reliability. This scale measures the strength, the sensation and, the qualitative and quantitative prehension. It is currently used as secondary outcomes in clinical trials and especially in the European Multicenter Study about Spinal Cord Injury (EMSCI) or in the Nogo Inhibition in Spinal Cord Injury (NISCI) study. (25)

5.9.2.4 Walking Index for Spinal Cord Injury measurement

Along the study, patients will experiment different kinds of functional improvements and some of them will be able to increment the locomotion. That's why it is interesting to assess widely the locomotion pattern as the result of the intervention, to observe the possible changes that can be observable at this level. The participants concerned by this assessment will more probably be the ones with AIS grades B, C or D and with a lower level of injury. Nevertheless, it still important to consider this assessment for all the participants as the AIS grades may change widely especially during the first weeks of the intervention. The tool that will be used to first define the locomotor pattern of the participant will be the Walking Index for Spinal Cord Injury (WISCI) (see annex 6), as it is a specific scale for SCI patients and it permits to grade the physical assistance and devices required for walking. (26)

5.9.2.5 10-meter walk test measurement

An assessment for walking speed will be the 10-meter walk test (10mWT) (see annex 7). This evaluation proof will concern patients with a minimum of gait and walking capacities. Moreover, this test requires more equipment (chronometer, clear pathway with marks) and can be done in an easier way with two examinators. Setting-up the test will consist on marking 10-meter pathways with landmarks at 2 meters, 8 meters and 10 meters. Then it will be asked to the participant to walk during the 10 meters at normal speed, and the examinator will record the time taken between the 2-meter line and the 8-meter line, while the other examinator can record the time of the total 10 meters to consider the acceleration. (27) In the present study, the 10 mWT will be repeated three time for each patient and the total average of the three trials will be recorded and compared between the different endpoints.

5.9.2.6 6-minute walking test measurement

On patient that possess correct walking capacities, it will be interesting to apply the 6-minutes walking test in order to measure the distance that a patient can run through, performing a quickly walk on a flat, hard surface during 6 minutes. This test will be self-paced, which mean that the patient will be authorized to choose its own intensity, pausing and resting during the test. Therefore, this proof will serve to assess the submaximal level that participant can have while performing functional activities. No specific devices are needed to perform this test, a single 30 meters pathways and a chronometer. (28) The distance performed will be registered and compared with the one obtained at different endpoints and with the other group of participants.

5.9.2.7 Quality of life

Assessing the quality-of-life improvement along the study will also be possible via the SF36 questionnaire (see annex 8). This Short Form Health Survey questionnaire possesses 36 items (SF-36) assessing the quality of life of the participants. It is a widely used tool among the investigation ambit and here a single scores of health-related quality of life "SF-36 Total/Global/Overall Score" will be reported as it is greatly reported in the literature. (29) Then the score evolution at SF-36 survey will be reported and interpreted.

5.9.3 Neurophysiological improvement

In order to extend the diagnosis of the participants undergoing the ATI355 application, neurophysiological outcomes can be evaluated. Before any neurophysiological assessment the SCI level was determined through the ISNCSCI guideline for each side of the participants bodies. (13,17) The neurophysiological measurement will not apply to patients that undergone the previous ISNCSCI evaluation, and in which any neurophysiological examination of lower limb will be considered useless by the investigator, due to a high grade of injury. However, the patients will be able to integrate the neurophysiological examination afterward during the study, if any lower limb improvement is observed at 3-month or 6-month timepoint (according to the investigator opinion).

5.9.3.1 Nerve conducting velocity

The nerve conducting velocity (NCV) proof help to elicit the presence of nerve activity and will be aimed to test the distal motor latency, the motor NCV and the compound motor action potential (CMAP) on the tibial nerves of both left and right bodysides. These measurements will be made via surface electrodes at a temperature of 30 degrees (with a warming lamp help). For the motor latency, the measurement will be made from the negative phase onset of the potential. (13,30)

5.9.3.2 Somatosensory evoked potentials

The somatosensory evoked potential (SSEP) test is a tool that record the integrity of the transmission of somatosensory nerve fibres impulse. It can be recorded at a spinal level as well as at peripheral level. It can assess the cervical level of SCI by stimulating the upper limb nerves and may predict hand function loss. As well as a stimulation of the tibial nerve that may predict a lower limb function recovery. Therefore, in the present study all participants will undergo this SSEP measurement to evaluate the amplitudes and the latencies of the ulnar and tibial nerves. (13,17) Data will be registered and interpreted at the different endpoints.

5.9.3.3 Motor evoked potentials

The motor evoked potentials (MEP) testing by transcortical magnetic stimulation can assess the extend and the level of SCI. The MEP will be recorded bilaterally at the level of the abductor digiti minimi muscle in order to predict hand function recovery. And also, the nerves fibres activity of both left and right tibialis anterior muscles in order to predict the ambulatory capacities. For all participants, the latencies and amplitudes for these muscles will be recorded. (13,17)

5.10 Assessments

From the beginning of the study, participants will be first recruited, then they will undergo the eligibility screening, and before the randomization and the group allocation, they will follow the baseline assessment. During the baseline assessment (week 0), all the outcomes (primary and secondary) will be evaluated to have references values. At 3-month of evolution there will be the final assessment of all the primary and secondary outcomes, there will be the first interpretation of the results obtained with the ones of the baseline. Then two follow-up periods will be applied, a midterm assessment at 6-month follow-up and a long-term assessment at 1-year follow-up, during which the totality of the outcomes will be assessed again.

5.11 Statistical Analysis

All patients who received i.t. catheterization or repeated bolus injections were included in the data analysis. The data analysis will be conducted through the “IBM SPSS Statistics” software. The normal distribution of the sample’s data will be verified via the normality proof of Kolmogorov-Smirnoff on SPSS, establishing the following hypothesis: H0: Data are distributed normally, so if $p>0.05$ the data follows a normal distribution in our population. The variables will be considered as parametric, so the following tests will be applied.

Firstly, the outcomes data will be compared among the two groups at a unique timepoint, then the following tests will be applied for each outcome:

- The data analysis of the different outcomes, the Improvement of the motor and sensory function according to the International Standards for the Neurological Classification of Spinal Cord Injury of traumatic acute SCI patients; the change on grade of functional independence, evaluated by the Functional Independence Measure and Functional Assessment Measure (FIM+FAM); the change on functioning, evaluated by the Spinal Cord Independence Measure (SCIM-III), the change on upper limb function, evaluated by the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP); and the change on the Walking Index for Spinal Cord Injury (WISCI) measurement, can all be categorized as a quantitative, discrete variable where two samples (Control and Experimental group) will be compared. So, the T-test will be applied for each of the outcomes assessed.
- Then the change on 10-meter walk test (10mWT) measurements; change on 6-minute walking test (6MWT) measurements; change on nerve conducting velocity; change on somatosensory evoked potentials; and the change on motor evoked potentials, can be considered as a quantitative continuous variable where the two samples will also be compared. Thus, a T-test will be applied again for each outcome analysed.
- The change on quality of life (SF36) will be considered as a qualitative ordinal variable. The values obtained for the two different groups will be compared between themselves, and a Chi-squared test will be applied.

Secondly, we can consider that the data of the assessed outcomes can be compared between the different endpoints, then other tests will be applied:

- The data analysis of the previous outcomes, the Improvement of the motor and sensory function according to the International Standards for the Neurological Classification of Spinal Cord Injury of traumatic acute SCI patients; the change on grade of functional independence, evaluated by the Functional Independence Measure and Functional Assessment Measure (FIM+FAM); the change on functioning, evaluated by the Spinal Cord Independence Measure (SCIM-III), the change on upper limb function, evaluated by the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP); and the change on the Walking Index for Spinal Cord Injury (WISCI) measurement, can all be categorized as a quantitative, discrete variable. Those outcomes will be evaluated and compared at four different endpoints (Baseline, 3-months, 6-months and 1-year); thus, an ANOVA test will be applied.
- Then the change on 10-meter walk test (10mWT) measurements; change on 6-minute walking test (6MWT) measurements; change on nerve conducting velocity; change on somatosensory evoked potentials; and the change on motor evoked potentials, can be considered as a quantitative continuous variable. And these outcomes will be evaluated and compared at the same four different endpoints. Thus, an ANOVA test will be applied for each outcome analysis.
- The change on quality of life (SF36) will be considered as a qualitative ordinal variable. It will be evaluated and compared at the four different endpoints between the two groups, so a Chi-squared test will be applied.

During this statistical analysis, the statistical significance level of α will be equal to 0.05 (5%) and the confidence interval (CI) will be equal to 0.95 (95%).

6 Ethics

This study will follow good and ethical clinical practice and will be conducted following the rules set in the Helsinki Declaration (World Medical Association, 1989). Informed written consent will be signed by all the participants.

7 Calendar

	Study Period						
	Enrolment	Allocation	Post-Allocation			Follow-up	
			Baseline	Intervention		Post-Intervention	
TIMEPOINT	Week -1		Week 0	Day 1 to 30	Day 31 to 90	6-month	1-year
ENROLMENT							
Eligibility Screening	x						
Informed consent	x						
Allocation		x					
INTERVENTIONS							
Control group							
- Placebo				x			
- Rehabilitation				←	→		
Experimental group							
- ATI355				x			
- Rehabilitation				←	→		
ASSESSMENTS							
Functional			x		x	x	x
Neurological			x		x	x	x
Neurophysiological			x		x	x	x

8 Discussion: Hoped results and improvement

The ATI355 treatment is hoped to be well tolerated by the participants. Following the study of K. Kucher et al. 2018, the ATI355 administrated via repeated intrathecal bolus injections and continuous intrathecal infusion was well tolerated in acute traumatic SCI patients. However, some adverse effects (AE) were observed during the study, but most of them were considered mild and few of them were related to the ATI355 administration. The most common AE reported was the headache, and it was considered as related with the intrathecal route of administration, due to a potential cerebrospinal fluid pressure lowering during the injection. Then, one case of bacterial meningitis has been reported and identified as related to the administration route. Therefore, there is a possible risk of infections when administrating the treatment in the intrathecal cavity, and this risk should be seriously considered. (13)

To consider the efficacy of the ATI355 treatment, the neurological level, the motor score and the sensory score must be compared over the different end points (baseline and 1-year). In fact, the control and experimental groups will be directly compared between themselves to observe any improvement related to the treatment. But it might not be sufficient as the improvement appears spontaneously in patients with acute traumatic SCI and it is impossible to predict if a patient in the experimental group strongly improves due to the ATI355 administration or any others reasons. (16) Moreover, there is the need to rely on universal and clinically studied values to make the results easier at interpretation and generalization.

Regarding the neurological improvement assessed with the ISNCSCI, it was reported that the rates of conversion can vary widely depending on the initial grading of the patients (AIS). Thus, it was observed that around 80% of the initially assessed AIS A patients remain as AIS A, while the spontaneous neurologic recovery at 1 year of patients graded AIS B that convert into AIS C was between 15 and 40%, and into AIS D was also reported to be as much as 40%. AIS C conversion to AIS D was reported to be between 60 and 80% of the whole sample of patients after one year. Also, we will consider that obtaining higher percentage of previous described improved neurological score during the first year (at final assessment) can possibly constitute a major neurological improvement possible to associate with the ATI355 injections. Moreover, it is important to specify that the use of AIS grades as the unique proof of beneficial ATI355 use cannot be statistically differentiated from the neurologic improvement related to the spontaneous recovery. In fact, it can appear as too ambitious to hope a AIS conversion of more than one grade as a threshold for demonstrating therapeutic efficacy. Thus, this grading system will unlikely predict a beneficial effect of the ATI355, but it can be used as a complementary information, to consider in combination with stronger outcomes.

Another outcome that can be predictive of ATI355 injection benefits is the motor recovery. In fact, the spontaneous motor recovery of SCI patient after 1 year has been stated to be 4.6 points for AIS A subjects, 31.3 points for AIS B subjects, and 12.9 motor points for AIS C and D subjects combined. So, if the patients of the experimental group show a greater improvement than the previously stated motor recovery punctuation, then it will be possible to confirm the beneficial effect of the intervention. Moreover, as with the AIS grades conversion, the AIS A patients will show a lower degrees of motor recovery than incomplete SCI patients.

The sensory recovery will be measured and an improvement of more than the spontaneous recovery level is hoped to confirm the efficacy of the intervention in the experimental group. Following the NASCIS study, the spontaneous recovery of sensory scores after 1 year for AIS A subjects is 5.5 points for light touch and 5.1 points for pinprick sensation, for AIS B subjects it is 10.8 for light touch and 15.8 for pinprick; while for AIS C and D subjects the improvement is 3.0 for light touch and 9.2 for pinprick. However, it is important to specify the limited sensitivity of the ASIA sensory scoring as it possess only three grades of evaluation (0: absent, 1: impaired and 2: normal). So, as with the AIS conversion the sensory improvement may bring few information regarding a possible improvement of the patients but it can nevertheless be used as a combination factor in addition with the others outcomes. (16)

And finally, to consider an improvement in the experimental group, the patients will need to obtain a minimal gain of 6 points for AIS A-B and 12 points for AIS C-D at the GRASSP assessment. (25)

In despite of the previously obtained values, it still being a real challenge to determine the minimal values that are needed to be obtained to confirm a beneficial therapeutic intervention. And nowadays

the best strategy to determine the benefit of an intervention is to correlate the structure or the function measure with a relevant activity outcome. (31) As obtaining a neurological improvement correlated with a meaningful functional benefit. Which mean that if the overall obtained data concerning the assessed outcomes (ISNCSCI, SCIM-III, FIM, WISCI…) correlates with an important positive change in function, then a clear benefit would be conclude. However, all the previously stated strategies need to be considered to consider any considerable improvement due to ATI355 injections in the experimental group.

Regardless to the possible relevance and interesting results that can give this study, it has been observed - in previous studies - the Nogo-A antibodies application in rehabilitative environment (treadmill training) on rats. It has been concluded from the results obtained, the interference that can cause a combination of those two specifics treatment. The behavioural and plasticity mechanisms that offers the Nogo-A antibodies application and treadmill training treatment are shown to be different. Moreover, a possible competitive effect was suggested between the mechanisms behind the administration of those two specifics treatments for the development of a movement patterns. However, if the combination of Nogo-A antibodies with treadmill rehabilitation may interfere on the stepping pattern, and give abnormal movement patterns on rats, it can be different on human. In fact, one possible explanation of these results can be due to the fact that this experiment has been conducted on animal subject, their specific rehabilitation (treadmill) and their spontaneous rehabilitation (normal rat movements) mixed, became competitive, and no constructive results were obtained as no specific instructions can be given to animal subjects. In contrary, human subject can be well oriented to follow a smart, logical and organized rehabilitation. Therefore, a deep understanding of each treatment effect of the individual and the possible effect that they can have the one on another is mandatory to design future studies protocol. (9,32)

Finally, the results obtained for the neurological assessment and the GRASSP measurement are expected to be above the minimal clinically studied values that will make the results become significant. Moreover, the values obtained in the experimental group, once compared with the one of the control group, are expected to be better, and demonstrate a significant improvement regarding the intervention. And the results registered at the different endpoints will also be compared, and are hoped to be better along the time progression.

9 Resources and funding

9.1 Resources

9.1.1 Material resources:

- ISNCSCI assessment kit material
- GRASSP kit
- “IBM SPSS Statistics” software
- Functional rehabilitative area

- 6 x 50 (300) ATI355 injection device and doses
- Chromometer
- Pen and paper
- Assessment scales
- 30-meter flat surface hallway
- Neurophysiological assessment devices for NCV, MEP and SSEP

9.1.2 Human resources:

A multidisciplinary team, composed of rehabilitative specialists and therapists, medical doctors, and qualified investigators.

9.1.3 Places resources:

Structure specialized in acute neurological rehabilitation able to respond the needs of this study protocol.

9.2 Funding

This study is considered as having an expensive cost and few funding options. Then the realisation of such protocol as the one stated before is hoped to be financed by granting, private donation or any other ethic financial sources.

10 Critical evaluation and conclusion of learning process

Realising this work was for me a real challenge, as it was the first time that I did not choose my subject of study. I had to read many scientific papers to learn more about the anti-Nogo therapy and understand in detail its effect on patients with SCI. It also permitted me to improve my skills in searching relevant bibliography. I clearly increase my general knowledges in neurorehabilitation field and implement my ambition in learning and keeping in touch with the future advanced therapies progress in SCI treatment. Moreover, I could link the current knowledge learned during the realisation of this project with the one taught in class of the master.

In conclusion, I consider this work as a great exercise for my future career as a physiotherapist, and I think it will help me not only for my future contribution to the investigation world but also to increase my personal knowledge by searching in scientific literature.

11 References

1. U.S. National Library of Medicine - ClinicalTrials.gov [Internet]. NISCI - Nogo Inhibition in Spinal Cord Injury (NISCI). 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03935321?term=NISCI&recrs=ab&rank=1#armgroup

2. James SL, Bannick MS, Montjoy-Venning WC, Lucchesi LR, Dandona L, Dandona R, et al. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(1):56–87.

3. Rowland JW, Hawryluk GWJ, Kwon B, Fehlings MG. Current status of acute spinal cord injury pathophysiology and emerging therapies: Promise on the horizon. Neurosurg Focus. 2008;25(5):1–3.

4. Yilmaz T, Kaptanoğlu E. Current and future medical therapeutic strategies for the functional repair of spinal cord injury. World J Orthop. 2015;6(1):42–55.

5. Rossignol S, Schwab M, Schwartz M, Fehlings MG. Spinal cord injury: Time to move? J Neurosci. 2007;27(44):11782–92.

6. Anjum A, Yazid MD, Daud MF, Idris J, Hwei Ng AM, Naicker AS, et al. Spinal cord injury: Pathophysiology, multimolecular interactions, and underlying recovery mechanisms. Int J Mol Sci. 2020;21(20):1–35.

7. Purves D, Augustine GJ, Fitzpatrick D, Hall WC, Lamantia A-S, Mooney RD, et al. Neuroscience. 6th editio. Purves D, Augustine GJ, Fitzpatrick D, Hall WC, Lamantia A-S, Mooney RD, et al., editors. New York, United States of America: Sinauer Associates Oxford University Press; 2018.

8. Aravamudhan S, Bellamkonda R V. Toward a convergence of regenerative medicine, rehabilitation, and neuroprosthetics. J Neurotrauma. 2011;28(11):2329–47.

9. Fawcett JW, Curt A. Damage control in the nervous system: Rehabilitation in a plastic environment. Nat Med [Internet]. 2009;15(7):735–6. Available from: http://dx.doi.org/10.1038/nm0709-735

10. Kempf A, Schwab ME. Nogo-A represses anatomical and synaptic plasticity in the central nervous system. Physiology. 2013;28(3):151–63.

11. Oertle T, Schwab ME. Nogo and its paRTNers. Trends Cell Biol. 2003;13(4):187–94.

12. Schwab ME, Strittmatter SM. Nogo limits neural plasticity and recovery from injury. Curr Opin Neurobiol. :53–60.

13. Kucher K, Johns D, Maier D, Abel R, Badke A, Baron H, et al. First-in-man intrathecal application of neurite growth-promoting anti-nogo- a antibodies in acute spinal cord injury. Neurorehabil Neural Repair. 2018;32(6–7):578–89.

14. Kwon BK, Sekhon LH, Fehlings MG. Emerging repair, regeneration, and translational research advances for spinal cord injury. Spine (Phila Pa 1976). 2010;35(21 SUPPL.):263–70.

15. Fouad K, Dietz V, Schwab ME. Improving axonal growth and functional recovery after experimental spinal cord injury by neutralizing myelin associated inhibitors. Brain Res Rev. 2001;36(2–3):204–12.

16. Fawcett JW, Curt A, Steeves JD, Coleman WP, Tuszynski MH, Lammertse D, et al. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: Spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. Spinal Cord. 2007;45(3):190–205.

17. Curt A, Dietz V. Electrophysiological recordings in patients with spinal cord injury: Significance for predicting outcome. Spinal Cord. 1999;37(3):157–65.

18. U.S. National Library Of Medicine - ClinicalTrials.gov [Internet]. European Multicentre Study of Human Spinal Cord Injury. 2012. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01571531

19. Nas K, Yazmalar L, Şah V, Aydin A, Öneş K. Rehabilitation of spinal cord injuries. World J Orthop. 2015;6(1):8–16.

20. Ahuja CS, Wilson JR, Nori S, Kotter MRN, Druschel C, Curt A, et al. Traumatic spinal cord injury. Nat Rev Dis Prim. 2017;3.

21. Whiteneck G, Gassaway J, Dijkers M, Backus D, Charlifue S, Chen D, et al. The SCIRehab project: treatment time spent in SCI rehabilitation. Inpatient treatment time across disciplines in spinal cord injury rehabilitation. J Spinal Cord Med. 2011;34(2):133–48.

22. Schuld C, Franz S, Brüggemann K, Heutehaus L, Weidner N, Kirshblum SC, et al. International standards for neurological classification of spinal cord injury: impact of the revised worksheet (revision 02/13) on classification performance. J Spinal Cord Med [Internet]. 2016;39(5):504–12. Available from: http://dx.doi.org/10.1080/10790268.2016.1180831

23. Wright J. Functional Independence Measure. In: Encyclopedia of Clinical Neuropsychology. 2011. p. 1112–3.

24. Walden K, Plashkes T, Sproule S, Morin C. Spinal Cord Independence Measure (SCIM): A clinical guideline for performing the SCIM III. Encycl Clin Neuropsychol. 2016;(February):3258–61.

25. Marino RJ, Sinko R, Bryden A, Backus D, Chen D, Nemunaitis GA, et al. Comparison of responsiveness and minimal clinically important difference of the capabilities of upper extremity test (CUE-T) and the graded redefined assessment of strength, sensibility and prehension (GRASSP). Top Spinal Cord Inj Rehabil. 2018;24(3):227–38.

26. Morganti B, Scivoletto G, Ditunno P, Ditunno JF, Molinari M. Walking index for spinal cord injury (WISCI): Criterion validation. Spinal Cord. 2005;43(1):27–33.

27. de Baptista CRJA, Vicente AM, Souza MA, Cardoso J, Ramalho VM, Mattiello-Sverzut AC. Methods of 10-Meter Walk Test and Repercussions for Reliability Obtained in Typically Developing Children. Rehabil Res Pract. 2020;2020:1–7.

28. Issues S, Test MW, Equipment R, Preparation P. American Thoracic Society ATS Statement : Guidelines for the Six-Minute Walk Test. 2002;166:111–7.

29. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. SAGE Open Med. 2016;4:205031211667172.

30. Kirshblum S, Lim S, Garstang S, Millis S. Electrodiagnostic changes of the lower limbs in subjects with chronic complete cervical spinal cord injury. Arch Phys Med Rehabil. 2001;82(5):604–7.

31. Wu X, Liu J, Tanadini LG, Lammertse DP, Blight AR, Kramer JLK, et al. Challenges for defining minimal clinically important difference (MCID) after spinal cord injury. Spinal Cord.

2015;53(2):84–91.

32. Maier IC, Ichiyama RM, Courtine G, Schnell L, Lavrov I, Edgerton VR, et al. Differential effects of anti-Nogo-A antibody treatment and treadmill training in rats with incomplete spinal cord injury. Brain. 2009;132(6):1426–40.

12 Annexes

Annex 1: American Spinal Injury Association Impairment Scale (AIS) – Classification system of SCI

A = Complete: No motor or sensory function is preserved in the sacral segments S4-S5

B = Incomplete: Sensory but not motor function is preserved below the neurological level and includes sacral segments S4-S5

C = Incomplete: Motor function preserved below the neurological level; more than half the key muscles below the neurological level have a muscle grade less than 3

D = Incomplete: Motor function preserved below the neurological level; at least half the key muscles below the neurological level have a muscle grade of 3 or more

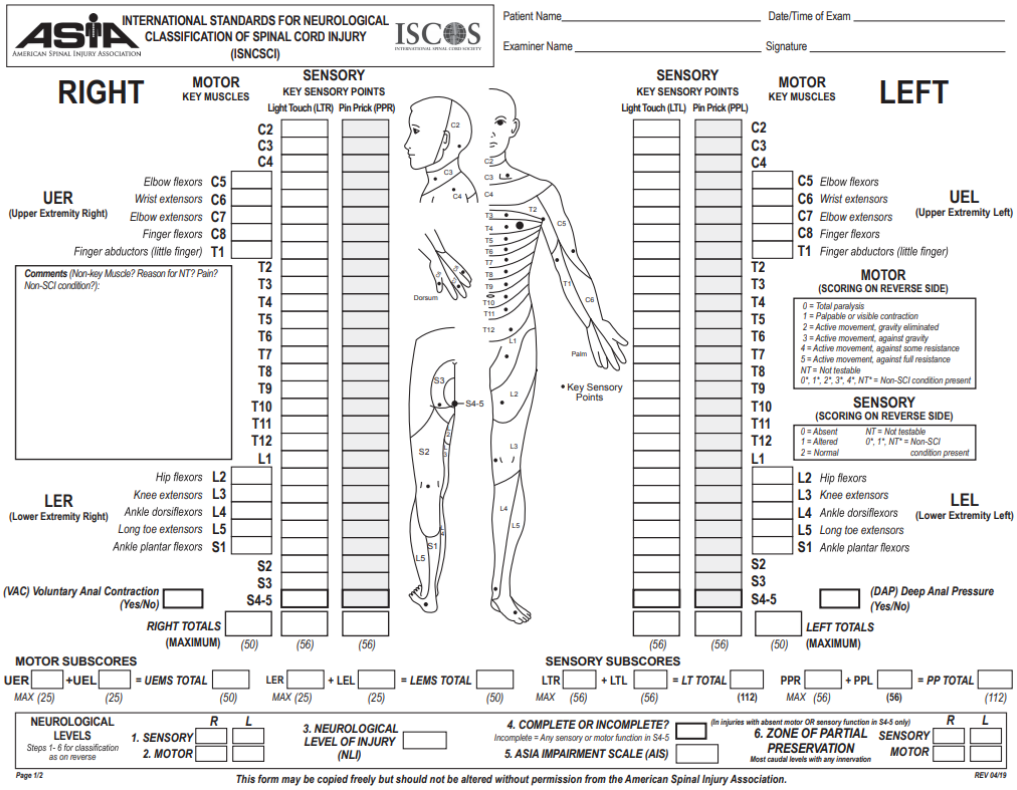
E = Normal: Motor and sensory function are normal

Annex 2: Calendar of compliance.

Intrathecal injections	**Injection 1:**	**Injection 2:**	**Injection 3:**	**Injection 4:**	**Injection 5:**	**Injection 6:**
Date						
Sign						
Functional rehabilitation						**# Session /week:**
Week 1						
Week 2						
Week 3						
Week 4						

Week 5						
Week 6						
Week 7						
Week 8						
Week 9						
Week 10						
Week 11						
Week 12						
Week 13						
Week 14						
						TOTAL:

Annex 3:



INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY (ISNCSCI)

Patient Name _____ Date/Time of Exam _____

Examiner Name _____ Signature _____

RIGHT — MOTOR KEY MUSCLES — SENSORY KEY SENSORY POINTS — Light Touch (LTR) Pin Prick (PPR)

LEFT — MOTOR KEY MUSCLES — SENSORY KEY SENSORY POINTS — Light Touch (LTL) Pin Prick (PPL)

UER (Upper Extremity Right): C5 Elbow flexors; C6 Wrist extensors; C7 Elbow extensors; C8 Finger flexors; T1 Finger abductors (little finger)

UEL (Upper Extremity Left): C5 Elbow flexors; C6 Wrist extensors; C7 Elbow extensors; C8 Finger flexors; T1 Finger abductors (little finger)

Comments (Non-key Muscle? Reason for NT? Pain? Non-SCI condition?):

C2 C3 C4 C5 C6 C7 C8 T1 T2 T3 T4 T5 T6 T7 T8 T9 T10 T11 T12 L1 L2 L3 L4 L5 S1 S2 S3 S4-5

LER (Lower Extremity Right): L2 Hip flexors; L3 Knee extensors; L4 Ankle dorsiflexors; L5 Long toe extensors; S1 Ankle plantar flexors

LEL (Lower Extremity Left): L2 Hip flexors; L3 Knee extensors; L4 Ankle dorsiflexors; L5 Long toe extensors; S1 Ankle plantar flexors

MOTOR (SCORING ON REVERSE SIDE)

0 = Total paralysis
1 = Palpable or visible contraction
2 = Active movement, gravity eliminated
3 = Active movement, against gravity
4 = Active movement, against some resistance
5 = Active movement, against full resistance
NT = Not testable
0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present

SENSORY (SCORING ON REVERSE SIDE)

0 = Absent NT = Not testable
1 = Altered 0*, 1*, NT* = Non-SCI condition present
2 = Normal

(VAC) Voluntary Anal Contraction (Yes/No)

(DAP) Deep Anal Pressure (Yes/No)

RIGHT TOTALS (MAXIMUM) (50) (56) (56)

LEFT TOTALS (MAXIMUM) (56) (56) (50)

• Key Sensory Points

MOTOR SUBSCORES: UER +UEL = UEMS TOTAL (MAX 25) (25) (50); LER + LEL = LEMS TOTAL (MAX 25) (25) (50)

SENSORY SUBSCORES: LTR + LTL = LT TOTAL (MAX 56) (56) (112); PPR + PPL = PP TOTAL (MAX 56) (56) (112)

NEUROLOGICAL LEVELS (Steps 1- 6 for classification as on reverse)
1. SENSORY R L
2. MOTOR R L
3. NEUROLOGICAL LEVEL OF INJURY (NLI)
4. COMPLETE OR INCOMPLETE? (Incomplete = Any sensory or motor function in S4-5)
5. ASIA IMPAIRMENT SCALE (AIS)
6. ZONE OF PARTIAL PRESERVATION (Most caudal levels with any innervation) (In injuries with absent motor OR sensory function in S4-5 only) SENSORY R L; MOTOR R L

Page 1/2

This form may be copied freely but should not be altered without permission from the American Spinal Injury Association.

REV 04/19

Muscle Function Grading

0 = Total paralysis

1 = Palpable or visible contraction

2 = Active movement, full range of motion (ROM) with gravity eliminated

3 = Active movement, full ROM against gravity

4 = Active movement, full ROM against gravity and moderate resistance in a muscle specific position

5 = (Normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person

NT = Not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)

0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present [a]

Sensory Grading

0 = Absent **1** = Altered, either decreased/impaired sensation or hypersensitivity

2 = Normal **NT** = Not testable

0*, 1*, NT* = Non-SCI condition present [a]

[a] Note: Abnormal motor and sensory scores should be tagged with a "*" to indicate an impairment due to a non-SCI condition. The non-SCI condition should be explained in the comments box together with information about how the score is rated for classification purposes (at least normal / not normal for classification).

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, adbuction, adduction, internal and external rotation **Elbow:** Supination	C5
Elbow: Pronation **Wrist:** Flexion	C6
Finger: Flexion at proximal joint, extension **Thumb:** Flexion, extension and abduction in plane of thumb	C7
Finger: Flexion at MCP joint **Thumb:** Opposition, adduction and abduction perpendicular to palm	C8
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation **Knee:** Flexion **Ankle:** Inversion and eversion **Toe:** MP and IP extension	L4
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments S4-5 by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3.

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.

AMERICAN SPINAL INJURY ASSOCIATION

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

INTERNATIONAL SPINAL CORD SOCIETY

Page 2/2

Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI).
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
*If voluntary anal contraction = **No** AND all S4-5 sensory scores = **0***
*AND deep anal pressure = **No**, then injury is **Complete.***
*Otherwise, injury is **Incomplete.***

5. Determine ASIA Impairment Scale (AIS) Grade.
Is injury Complete? If YES, AIS=A
NO ↓
Is injury Motor Complete? If YES, AIS=B
NO ↓ (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)
Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?
NO ↓ AIS=C
YES ↓ AIS=D
If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact and the ASIA Impairment Scale does not apply.

6. Determine the zone of partial preservation (ZPP).
The ZPP is used only in injuries with absent motor (no VAC) OR sensory function (no DAP, no LT and no PP sensation) in the lowest sacral segments S4-5, and refers to those dermatomes and myotomes caudal to the sensory and motor levels that remain partially innervated. With sacral sparing of sensory function, the sensory ZPP is not applicable and therefore "NA" is recorded in the block of the worksheet. Accordingly, if VAC is present, the motor ZPP is not applicable and is noted as "NA".

Annex 4:

FUNCTIONAL INDEPENDENCE MEASURE™ AND FUNCTIONAL ASSESSMENT MEASURE
Brain Injury

Scale:
7 Complete Independence (timely, safely)
6 Modified Independence (extra time, devices)
5 Supervision (cuing, coaxing, prompting)
4 Minimal Assist (performs 75% or more of task)
3 Moderate Assist (performs 50%-74% of task)
2 Maximal Assist (performs 25% to 49% of task)
1 Total Assist (performs less than 25% of task)

(Patient Stamp)

	SELF CARE ITEMS	Adm	Goal	D/C	F/U
1.	Feeding				
2.	Grooming				
3.	Bathing				
4.	Dressing Upper Body				
5.	Dressing Lower Body				
6.	Toileting				
7.	Swallowing*				
	SPHINCTER CONTROL				
8.	Bladder Management				
9.	Bowel Management				
	MOBILITY ITEMS (Type of Transfer)				
10.	Bed, Chair, Wheelchair _____				
11.	Toilet _____				
12.	Tub or Shower _____				
13.	Car Transfer* _____				
	LOCOMOTION				
14.	Walking/Wheelchair (circle)				
15.	Stairs				
16.	Community Access*				
	COMMUNICATION ITEMS				
17.	Comprehension-Audio/Visual (circle)				
18.	Expression-Verbal, Non-Verbal (circle)				
19.	Reading*				
20.	Writing*				
21.	Speech Intelligibility*				
	PSYCHOSOCIAL ADJUSTMENT				
22.	Social Interaction				
23.	Emotional Status*				
24.	Adjustment to Limitations*				
25.	Employability*				
	COGNITIVE FUNCTION				
26.	Problem Solving				
27.	Memory				
28.	Orientation*				
29.	Attention*				
30.	Safety Judgement*				

*FAM items

	Admt	Date	D/C	Date		Admt	Date	D/C	Date
RN	_____	_____	_____	_____	ST	_____	_____	_____	_____
PT	_____	_____	_____	_____	PSY	_____	_____	_____	_____
OT	_____	_____	_____	_____	REC	_____	_____	_____	_____

Annex 5:

FACILITY NAME

SCIM – Spinal Cord Independence Measure
(Version III, Self-report 2013)

ADDRESSOGRAPH

This section asks about functioning in activities of daily living. For each item, please check the box next to the statement that best reflects **your current situation**. Please read the text carefully and only check one box in each section.

1. Eating and drinking

0. I need artificial feeding or a stomach tube
0. I need total assistance with eating/drinking
1. I need partial assistance with eating/drinking or for putting on/taking off adaptive devices
2. I eat/drink independently, but I need adaptive devices or assistance for cutting food, pouring drinks or opening containers
3. I eat/drink independently without assistance or adaptive devices

2. (a) Washing your upper body and head

Washing your upper body and head includes soaping and drying, and using a water tap.

0. I need total assistance
1. I need partial assistance
2. I am independent but need adaptive devices or specific equipment (e.g., bars, chair)
3. I am independent and do not need adaptive devices or specific equipment

(b) Washing your lower body

Washing your lower body includes soaping and drying, and using a water tap.

0. I need total assistance
1. I need partial assistance
2. I am independent but need adaptive devices or specific equipment (e.g., bars, chair)
3. I am independent and do not need adaptive devices or specific equipment

3. (a) Dressing your upper body

Dressing the upper body includes putting on and taking off clothes like t-shirts, blouses, shirts, bras, shawls, or orthoses (e.g., arm splint, neck brace, corset)

Easy-to-dress clothes are those without buttons, zippers, or laces.

Difficult-to-dress clothes are those with buttons, zippers, or laces.

0. I need total assistance
1. I need partial assistance, even with easy-to-dress clothes
2. I do not need assistance with easy-to-dress clothes, but I need adaptive devices or specific equipment
3. I am independent with easy-to-dress clothes and only need assistance or adaptive devices or a specific setting with difficult-to-dress clothes
4. I am completely independent

FACILITY NAME

SCIM – Spinal Cord Independence Measure
(Version III, Self-report 2013)

ADDRESSOGRAPH

(b) Dressing your lower body

Dressing the lower body includes putting on and taking off clothes like shorts, trousers, shoes, socks, belts, or orthoses (e.g., leg splint)

Easy-to-dress clothes are those without buttons, zippers, or laces.

Difficult-to-dress clothes are those with buttons, zippers, or laces.

0. I need total assistance
1. I need partial assistance, even with easy-to-dress clothes
2. I do not need assistance with easy-to-dress clothes, but I need adaptive devices or specific equipment
3. I am independent with easy-to-dress clothes and only need assistance or adaptive devices or a specific setting with difficult-to-dress clothes
4. I am completely independent

4. Grooming

Please think about activities such as washing hands and face, brushing teeth, combing hair, shaving, or applying makeup

0. I need total assistance
1. I need partial assistance
2. I am independent with adaptive devices
3. I am independent without adaptive devices

5. Breathing

Please check only one box, depending on whether or not you need a respiratory (tracheal) tube.

I need a respiratory (tracheal) tube...

0. as well as permanent or from time to time assisted ventilation
2. as well as extra oxygen and a lot of assistance in coughing or respiratory tube management
4. as well as little assistance in coughing or respiratory tube management

I do not need a respiratory (tracheal) tube...

6. but I need extra oxygen or a lot of assistance in coughing or a mask (e.g., positive end-expiratory pressure (PEEP)) or assisted ventilation from time to time (e.g., bilevel positive airway pressure (BIPAP))
8. and only little assistance or stimulation for coughing
10. and can breathe and cough independently without any assistance or adaptive device

FACILITY NAME

SCIM – Spinal Cord Independence Measure
(Version III, Self-report 2013)

ADDRESSOGRAPH

6. Bladder management

Please think about the way you empty your bladder. [Scoring of item 6: see appendix A]

(a) Use of an indwelling catheter

0. Yes → Please go to question 7a
1. No → Please also answer questions 6b and 6c

(b) Intermittent catheterization

0. I need total assistance
1. I do it myself with assistance (self-catheterization)
2. I do it myself without assistance (self-catheterization)
3. I do not use it

(c) Use of external drainage instruments (e.g., condom catheter, diapers, sanitary napkins)

0. I need total assistance for using them
1. I need partial assistance for using them
2. I use them without assistance
3. I am continent with urine and do not use external drainage instruments

7. Bowel management *[scoring of item 7: see appendix B]*

(a) Do you need assistance with bowel management (e.g., for applying suppositories)?

0. Yes
1. No

(b) My bowel movements are...

0. irregular or seldom (less than once in 3 days)
1. regular (at least once every 3 days)

(c) Faecal incontinence ('accidents') happens...

0. twice a month or more
1. once a month
2. not at all

FACILITY NAME

SCIM – Spinal Cord Independence Measure
(Version III, Self-report 2013)

ADDRESSOGRAPH

8. Using the toilet

Please think about the use of the toilet, cleaning your genital area and hands, putting on and taking off clothes, and the use of sanitary napkins or diapers.

0. I need total assistance
1. I need partial assistance and cannot clean myself
2. I need partial assistance but can clean myself
4. I do not need assistance but I need adaptive devices (e.g., bars) or a special setting (e.g., wheelchair accessible toilet)
5. I do not need any assistance, adaptive devices or a special setting

9. How many of the following four activities can you perform without assistance or electrical aids

- ***turning your upper body in bed***
- ***turning your lower body in bed***
- ***sitting up in a bed***
- ***doing push-ups in wheelchair (with or without adaptive devices)***

0. none, I need assistance in all these activities
2. one
4. two or three
6. all of them

10. Transfers from the bed to the wheelchair

0. I need total assistance
1. I need partial assistance, supervision or adaptive devices (e.g., sliding board)
2. I do not need any assistance or adaptive devices
2. I do not use a wheelchair

11. Transfers from the wheelchair to the toilet/tub

Transferring also includes transfers from the wheelchair or bed to a toilet wheelchair

0. I need total assistance
1. I need partial assistance, supervision or adaptive devices (e.g., grab-bars)
2. I do not need any assistance or adaptive devices
2. I do not use a wheelchair

FACILITY NAME

SCIM – Spinal Cord Independence Measure
(Version III, Self-report 2013)

ADDRESSOGRAPH

12. Moving around indoors

Please check only one box, depending on whether or not you usually use a wheelchair or walk to move around indoors.

I use a wheelchair. To move around, I...

0. need total assistance
1. need an electric wheelchair or partial assistance to operate a manual wheelchair
2. am independent in a manual wheelchair

I walk indoors and I...

3. need supervision while walking (with or without walking aids)
4. walk with a walking frame or crutches, swinging forward with both feet at a time
5. walk with crutches or two canes, setting one foot before the other
6. walk with one cane
7. walk with a leg orthosis(es) only (e.g., leg splint)
8. walk without walking aids

13. Moving around moderate distances (10 to 100 metres)

Please check only one box, depending on whether or not you usually use a wheelchair or walk to move around moderate distances (10 to 100 meters).

I use a wheelchair. To move around, I...

0. need total assistance
1. need an electric wheelchair or partial assistance to operate a manual wheelchair
2. am independent in a manual wheelchair

I walk moderate distances and I...

3. need supervision while walking (with or without walking aids)
4. walk with a walking frame or crutches, swinging forward with both feet at a time
5. walk with crutches or two canes, setting one foot before the other
6. walk with one cane
7. walk with a leg orthosis(es) only (e.g., leg splint)
8. walk without walking aids

FACILITY NAME

SCIM – Spinal Cord Independence Measure
(Version III, Self-report 2013)

ADDRESSOGRAPH

14. Moving around outdoors for more than 100 metres

Please check only one box, depending on whether or not you usually use a wheelchair or walk to move around outdoors for more than 100 metres.

I use a wheelchair. To move around, I...

0. need total assistance
1. need an electric wheelchair or partial assistance to operate a manual wheelchair
2. am independent in a manual wheelchair

I walk more than 100 metres and I...

3. need supervision while walking (with or without walking aids)
4. walk with a walking frame or crutches, swinging forward with both feet at a time
5. walk with crutches or two canes, setting one foot before the other
6. walk with one cane
7. walk with a leg orthosis(es) only (e.g., leg splint)
8. walk without walking aids

15. Going up and down stairs

Please check only one box, depending on whether or not you are able to go up and down stairs.

0. I am unable to go up and down stairs

I can go up and down at least 3 steps...

1. but only with assistance or supervision
2. but only with devices (e.g., handrail, crutch or cane)
3. without any assistance, supervision or devices

16. Transfers from the wheelchair into the car

Transfers also include putting the wheelchair into and taking it out of the car.

0. I need total assistance
1. I need partial assistance, supervision or adaptive devices
2. I do not need any assistance or adaptive devices
2. I do not use a wheelchair

FACILITY NAME

SCIM – Spinal Cord Independence Measure
(Version III, Self-report 2013)

ADDRESSOGRAPH

17. Transfers from the floor to the wheelchair

0. I need assistance
1. I do not need any assistance
1. I do not use a wheelchair

SCORING (for clinician to complete)

Please use the following tables for items 6 and 7.

Item 6

SCIM-SR Item			Score in SCIM-SR
6A	6B Not relevant if 6A=0	6C Not relevant if 6A=0	
0			0
1	0	0	6
1	0	1	6
1	0	2	6
1	0	3	6
1	1	0	6
1	1	1	6
1	1	2	6
1	1	3	6
1	2	0	6
1	2	1	6
1	2	2	9
1	2	3	11
1	3	0	6
1	3	1	6
1	3	2	13
1	3	3	15

Item 7

SCIM-SR Item			Score in SCIM-SR
7A Not relevant if 7B=0	7B	7C Not relevant if 7B=0	
	0		0
0	1	1	5
0	1	2	5
1	1	1	8
1	1	2	10
0	1	0	5
1	1	0	5

Self-care subscale, Items 1-4 (0-20) ☐

Respiration and sphincter management subscale, Items 5-8 (0-40) ☐

Mobility subscale, Items 9-17 (0-40) ☐

TOTAL SCIM SCORE (0-100) ☐

Date SCIM Completed: ☐☐☐☐ / ☐☐ / ☐☐
YYYY MM DD

Enter as much of the date as is known. If no details available, check Unknown.

☐ Unknown

Clinician Name/Signature: _____

Annex 6: Picture from Morganti B. et al. in "Walking index for spinal cord injury (WISCI): Criterion validation". Spinal Cord. 2005;43(1):27–33.

Table 1 Walking Index for Spinal Cord Injury (WISCI II)

Level	*Description*
00	Patient is unable to stand and/or participate in assisted walking.
01	Ambulates in parallel bars, with braces and physical assistance of two persons, less than 10 m.
02	Ambulates in parallel bars, with braces and physical assistance of two persons, 10 m.
03	Ambulates in parallel bars, with braces and physical assistance of one person, 10 m.
04	Ambulates in parallel bars, no braces and physical assistance of one person, 10 m.
05	Ambulates in parallel bars, with braces and no physical assistance, 10 m.
06	Ambulates with walker, with braces and physical assistance of one person, 10 m.
07	Ambulates with two crutches, with braces and physical assistance of one person, 10 m.
08	Ambulates with walker, no braces and physical assistance of one person, 10 m.
09	Ambulates with walker, with braces and no physical assistance, 10 m.
10	Ambulates with one cane/crutch, with braces and physical assistance of one person, 10 m.
11	Ambulates with two crutches, no braces and physical assistance of one person, 10 m.
12	Ambulates with two crutches, with braces and no physical assistance, 10 m.
13	Ambulates with walker, no braces and no physical assistance, 10 m.
14	Ambulates with one cane/crutch, no braces and physical assistance of one person, 10 m.
15	Ambulates with one cane/crutch, with braces and no physical assistance, 10 m.
16	Ambulates with two crutches, no braces and no physical assistance, 10 m.
17	Ambulates with no devices, no braces and physical assistance of one person, 10 m.
18	Ambulates with no devices, with braces and no physical assistance, 10 m.
19	Ambulates with one cane/crutch, no braces and no physical assistance, 10 m.
20	Ambulates with no devices, no braces and physical assistance, 10 m.

Annex 7: Picture from de Baptista CRJA et al. in "Methods of 10-Meter Walk Test and Repercussions for Reliability Obtained in Typically Developing Children". Rehabil Res Pract. 2020;2020:1–7.

Annex 8:

Today's date:____/____/____ ID No:__ __ __ __ __ __

First name:_____ Surname: _____

SF-36 Questionnaire

This questionnaire asks for your views about your health. For ALL questions, please tick, cross or colour the circle that most closely matches your response. There are no right or wrong answers. Please answer ALL questions.

1. In general, would you say your health is:	Poor	Fair	Good	Very good	Excellent
2. Compared to one year ago, how would you rate your health general in now?	Much worse now than one year ago	Somewhat worse than one year ago	About the same as one year ago	Somewhat better than one year ago	Much better than one year ago

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	No, not limited at all	Yes, limited a little	Yes, limited a lot
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports			
b. Moderate activities, such as moving a table pushing a vacuum cleaner, bowling, or playing			
c. Lifting or carrying groceries			
d. Climbing several flights of stairs			
e. Climbing one flight of stairs			
f. Bending, kneeling or stooping			
g. Walking more than a mile			
h. Walking several blocks			
i. Walking one block			
j. Bathing or dressing yourself			

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other daily activities as a result of your physical health?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Cut down on the amount of time you spent on work or other activities					
b. Accomplished less than you would like					
c. Were limited in the kind of work or other activities					
d. Had difficulty performing the work or other activities (e.g. it took extra effort)					

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Cut down on the amount of time you spent on work or other activities					
b. Accomplished less than you would like					
c. Did work or other activities less carefully than usual					

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	All of the time

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A liitle bit	Moderately	Quite a bit	Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. did you feel full of life?					
b. have you been very nervous?					
c. have you felt so down in the dumps that nothing could cheer you up?					
d. have you felt calm and peaceful?					
e. did you have a lot of energy?					
f. have you felt downhearted and depressed?					
g. did you feel worn out?					
h. have you been happy?					
i. did you feel tired?					

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

None of the time	A little of the time	Some of the time	Most of the time	All of the time

11. How TRUE or FALSE is each of the following statements for you?

	Defintely false	Mostly false	Don't know	Mostly true	Definitely true
a. I seem to get sick a little easier than other people					
b. I am as healthy as anybody I know					
c. I expect my health to get worse					
d. My health is excellent					