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Spinal Cord Injury: A Review of Current Management Considerations and Emerging Treatments

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Abstract

Traumatic spinal cord injuries can have devastating outcomes for patients. In this focused review, we discuss the epidemiology of spinal cord injuries, associated neurologic exam findings, and primary and secondary injury progression. We then delve into the emerging treatment approaches and relevance to improving outcomes. The disease is multifactorial and has many management considerations. This concise user-friendly resource can help guide clinicians caring for these patients. Also, it points to the need for continued scientific discovery and improved pharmaceutical and device innovations.

Keyywords

Spinal cord injuries; Treatment approaches; Neuroinflammation

Introduction

Traumatic spinal cord injuries (SCI) represent a serious and often irreversible neurological injury and can leave affected patients with catastrophic consequences to their quality of life. While there are several etiologies that can damage the spinal cord such as spinal tumors, demyelinating disorders, and infectious processes, trauma (particularly motor vehicle accidents) remains the most common mechanism of SCI in over 90% of cases. In 2020, there were nearly 18,000 newly reported cases of SCI1. In the USA alone, there are more than 300,000 people living with SCI [1]. Most SCI occur in males with a median age of ~43 years [2]. It is estimated that the lifetime costs associated with patients who have suffered from traumatic SCI ranges from 1.6 to 4.8 million US dollars1. Resulting clinical sequalae can include impaired sensation and motor deficits in addition to autonomic dysfunction. It is also associated with highly increased mortality by secondary causes such as respiratory infections, renal failure, and in some circumstances suicide [3]. The resulting prognosis varies greatly and is influenced by the cause of the injury, neurological level and the extent of damage, and resulting surgical and medical interventions.

Neurological Exam and Diagnosis of SCI

Initial workup often and at some point, during a patient's hospital course includes computed tomography (CT) and/or magnetic resonance imaging (MRI) to assess severity and guide management decisions [4]. MRI however serves as the gold standard for imaging of spinal cord injuries. Depending on the mechanism of injury, patients must often be surgically and medically stabilized before a reliable neurological exam can be conducted. Ideally, the patient should be able to cooperate with the examiner and follow their basic instructions to the best of their abilities for an exam to be deemed reliable. There currently exist several scales that have been utilized to assess spinal cord injury and determine prognosis of patients with SCI, with the American Spinal Injury Association Impairment scale being the current clinical favorite.

American Spinal Injury Association (ASIA) Impairment Scale (AIS)

The ASIA impairment scale represents a standardized examination that incorporates motor, sensory, and anorectal examination with dermatomal consideration [5,6]. A total of 28 different dermatomes are assessed bilaterally with light touch and pinprick sensation. A score of 0, 1, or 2 is given for either no sensation, altered sensation, or normal sensation, respectively. Final scores for this section of the ASIA scale can range from 0 to 224 (representing a normal sensory examination). The motor component of the exam grades five muscle groups in both the upper and lower extremities. The motor exam assesses motor function associated with the C5-T1 nerve roots in the upper extremity and the L2-S1 nerve roots in the lower extremity. Muscle strength is graded on the conventional 0 to 5 scale with 0 indicating paralysis and 5 indicating active, full range of motion against gravity (normal). This scale also takes into account the level of the spinal injury and whether the injury is complete or incomplete. Complete spinal cord injury requires evidence of complete loss of motor and sensory functions below the level of the lesion. These results are graded with a scale ranging from AIS Grade of A to E, with A signifying complete loss of motor or sensory function in the sacral segments and E signifying normal motor and sensory function below the lesion.

While the ASIA scale only assesses acute impairment, its prognostic value has been detailed in several studies [7-9]. In a report by Middendorp et al. found that grades A, B, C, and D correlated with significantly different outcomes in regards to a patient's ability to regain ambulatory function (p<0.001)⁷. Despite its prognostic ability, limitations exist with the ASIA scale as it does not assess anatomical implications of injury nor predicts other neurological sequalae of SCI. Furthermore, there is not enough evidence in the literature that differences in scores can or should be used to inform clinical decision making in regards to medical or surgical intervention [10]

Frankel scale

The Frankel scale was previously utilized as a severity scale for SCI11. It was based on a 5-point scale (ranging from Grade A to E) that assesses motor function below the level of the lesion. Scores ranged from Grade A to E, with each score differing by varying levels of useful motor strength. In its conception, this provided a simple and standardized method for comparing SCI, but has since fallen out of favor with the development of the ASIA impairment scale.

Primary and secondary phases of SCI

SCI can be classified into two phases of injury: primary and secondary. Primary injury results from the initial blunt force trauma to the spinal cord, affecting the neurons and glial cells at the location [12]. Blunt spinal cord injury (BSCI) and penetrating spinal cord injury (PSCI) are the most common types of injuries that are seen among patients [13]. BSCI results from falls and motor vehicle accidents, while PSCI are often a result of gunshot and stab wounds [13]. The vast majority of SCI can be attributed to blunt force trauma affecting the cervical spinal levels [13]. As a result of the initial trauma to the spinal cord, blood vessels rupture and disturb the blood flow and perfusion leading to ischemia, oxidative damage and edema; ultimately leading to cellular death [14]. Excitotoxity has also been seen minutes after trauma, leading to increased levels of glutamate which in turn increases the depolarization of nearby neurons [15]. An increase in neuronal depolarization results in an increase in intracellular calcium which can damage the neuronal mitochondria by inhibiting the sodium/potassium ATPases [14,15]. Excess calcium also affects the integrity of the cell via inducing the activation of cytosolic proteases like calpain, a calcium-dependent cysteine protease whose function is to attack the cell's cytoskeleton element spectrin, among a host of other endogenous proteins [15].

The secondary phase of injury is triggered by the death of glial cells and ischemia at the site of trauma. Vascular permeability in the primary injury phase allows for the infiltration of immune cells to the site of inflammation [16]. The characteristics of secondary injury are microglia and macrophage activation, neuroinflammation enhanced by reactive oxidants and upregulation of pro-inflammatory cytokines [17]. Microglial cells are part of the innate immune system in the central nervous system (CNS) that express chemokines and release pro-inflammatory cytokines that contribute to the persistent inflammation seen at the site of the lesion [18]. The release of pro-inflammatory cytokines and chemokines from the spinal cord cells in and around the trauma lesion begins the inflammatory cascade [19]. At the site, neutrophils secrete reactive oxygen species (ROS) and proteolytic enzymes for aseptic inflammation, but overstimulation of these reactive oxidants and enzymes leads to tissue damage [19,20]. Resident

microglia, and peripheral macrophages arrive next and are activated by neutrophil's effector functions and the upregulation of pro-inflammatory cytokines [16,21]. Activated microglia undergo a phenotypic change that induces the release of IL-1, IL-6, and TNF- α , all upregulated pro-inflammatory cytokines that inhibit nerve and synapse repair [18]. As microglia release neurotoxic molecules, like nitric oxide, macrophages are then activated and polarize to an M1, pro-inflammatory state [16]. Characteristics of M1 macrophages are release a significant amount of pro-inflammatory cytokines and inducing the release of metalloproteinases, collagenases, and furin (a protease enzyme) that mediates degradation of the cell's extracellular matrix [19]. TNF- α is also highly expressed when iron from the initial trauma accumulates in macrophages and prevents the conversion from the polarized state of M1 to an antiinflammatory M2 [16]. The secondary injury caused by these inflammatory processes can last for up to months after the initial trauma and because of this, motor and sensory functions deteriorate and become irreversible if there is no inflammatory intervention.

Surgical Management and Timing

The main surgical intervention for spinal cord injury (SCI) involves spinal decompression, which aims to relieve the pressure on spinal microvascular circulation that often occurs from blunt spinal trauma. By relieving the pressure, the hope is to reduce hypoxia and ischemia [22], thereby reducing the extent of secondary injury due to an improved vascular blood supply [23]. Decompressive surgery is indicted for SCI when the patient shows signs of progressive neurological impairment, partial SCI (not a complete Grade A SCI), and a fracture that is not amenable to a closed reduction [24]. The general consensus is that early intervention (within 8-24 hours after injury) after a partial SCI injury correlates with better patient outcomes [25-27], although evidence is limited. While studies have confirmed overall benefits (such as decreased pulmonary morbidity/duration of mechanical ventilation, decreased ICU stay, and decreased overall hospital stay) [28,29], not all studies have shown clear benefits in terms of long-term neurological improvement [30].

It is known that the level of the neurological insult correlates to the patient's potential for recovery [31]. There are studies that separate patient cases by cervical vs thoracolumbar injuries, which generally poses better evidence for cervical cases in terms of patient recovery post-surgical decompression [32]. However, in regards to when post-injury surgery would be most appropriate, there is not sufficient data stratifying patient cases based on neurological level or injury severity. In fact, when assessing severity of injury, surgical decompression has not shown any significant improvements overall for Grade A injuries (based on the ASIA scale), regardless of the timing of intervention [32-34]. This is supported by biological reasoning, as complete SCI indicates that the injury might be so severe that any neuroprotective intervention will not result in meaningful improvements via standard neurological patient assessments.

In regards to optimal timing of surgical intervention, the main thresholds currently reported in literature can be broken down into an ultra-early period (8-12 hours), an early period (within 24 hours), and a later period (48-72 hours) post-injury. It is important to note that these thresholds do not hold intrinsic biological relevance but are simply values chosen for practical implementation [32]. Clinical studies done thus far point to the two earlier time thresholds (<24 hours) as having the greatest potential for improved outcomes [30,35,36]. The late threshold does not seem to confer much advantage [37]. This is

supported by preclinical models which have provided evidence that the extent and duration of cord compression correlates with neurologic deficit [38,39]. In terms of human clinical trials, a major trial was the Surgical Timing in Acute Spinal Cord Injury Study, which observed patients with cervical SCI that underwent decompression within 24 hours after injury. Patients were twice as likely to have an improvement of 2 grades in the ASIA scale with similar rates of complication observed in both groups [40]. This was confirmed with another study in Canada after adjusting for pre-op status and neurological level of injury [30]. Taken together, these studies supported the concept of "Time is Spine," emphasizing the importance of early diagnosis and intervention to enhance long-term outcomes [23]. While these studies looked at outcomes of surgical intervention within 24 hours after injury, they did not examine ultra-early surgical intervention (<8-12 hours). The logistics of hospital location, protocols, and other factors such as the need for patient stabilization (in the case of catastrophic injury) make this practically difficult to implement, which might explain the dearth in such studies. However, the SCI-POEM study which was proposed in 2012, is a multicenter study aimed at identifying outcomes of patients undergoing surgical decompression <12 hours (Cohort 1) or >12 hours but <14 days (Cohort 2) after spinal cord injury [41]. The results are expected soon, which will help clarify any potential benefits of this early cutoff [32,41]. Overall, further research is needed to determine benefits of surgical intervention, stratified based on neurological level and injury severity, and the benefits of earlier intervention.

Medical Management

In acute SCI medical management has become the mainstay of treatment alongside surgical intervention in improving patient outcomes. Medical management for acute SCI includes early augmentation of mean arterial blood pressure (MAP) [26], intensive care unit (ICU) management [42], and prevention of secondary complications during a patient's hospital course.

Avoidance of hypotension and strictly adhering to blood pressure targets in patients with acute SCI serves to maintain adequate cerebral perfusion pressure and prevent secondary neuronal injury [43]. Optimal spinal cord perfusion is accomplished with a MAP goal of 85 to 90 mmHg. Based upon recommendations from the American Association of Neurological Surgeons MAP goals should be maintained for the first 7 days following initial injury [44]. Control of MAP is accomplished with vasopressors. Dopamine has been widely used for MAP augmentation; however, it has fallen out of favor with recent studies demonstrating better physiologic response to other vasopressors such as norepinephrine and phenylephrine. Both decrease the lactate-to-pyruvate ratio indicative of cell injury and death, however phenylephrine has been associated with a greater incidence of injury hemorrhage, further supporting primarily using norepinephrine for MAP augmentation [26].

While patients who suffer from acute SCI are hospitalized, they will also require intensive care management. Such care requires prophylaxis against deep vein thrombosis (DVT) and pulmonary embolisms within the first week after initial injury [45]. The risk for these venous thromboembolic complications is increased in patients of increasing ages or those with other injuries such as intracranial injury or long bone fracture [46]. Low molecular weight heparin (LMWH) enoxaparin (30 mg

subcutaneously, every 12 hours) is commonly used as DVT prophylaxis and has demonstrated superiority over standard low-dose unfractionated heparin (500 units subcutaneously, every 12 hours) in a large randomized controlled trial [47]. The recommended duration of DVT prophylaxis is 8-12 weeks and further depends upon the extent of injury [42]. In patients that have contraindications to pharmacologic DVT prophylaxis, inferior vena cava (IVC) filters are a suitable intervention. Prophylactic use of IVC filters may decrease the rate of pulmonary embolism in patients with SCI [48] as well as those with traumatic injury [49]. Following an acute SCI, patients may also have concomitant accessory muscle and diaphragm paralysis. Additionally, decreased strength of the abdominal muscles recruited in forced expiration results in diminished ability to cough and clear secretions. This places patient at increased risk for pneumonia, mucus plugging, and hypoventilation. To prevent these complications patients with SCI often require mechanical ventilation. A majority of patients with cervical acute SCI will need intubation and mechanical ventilation while hospitalized [50] however the need for ventilation may decrease as the patient recovers vital capacity which can take up to 3 months in most cases [51].

Use of steroids was also once commonplace, but the benefits steroids have on decreasing inflammation are limited by severe systemic side effects [20]. It is believed that systemic steroids such as methylprednisolone (MP) upregulate autoinflammatory factors and reduce oxidative insult. This results in prevention of intracellular potassium depletion, inhibition of lipid peroxidation and overall reduction of edema [24,52]. There has been a lack of studies showing that corticosteroids provide clinically relevant improvements in neurological outcomes, however. The lack of proven efficacy coupled with the increased risk of complications including surgical site infection, sepsis, poor wound-healing, peptic ulcer disease, hyperglycemia, gastrointestinal hemorrhage, respiratory infection, and lipid profile changes in has led to the existing guidelines recommending against the use of corticosteroids in acute SCI [53-55]. Despite being extensively investigated, the use of steroids remains a point of contention among clinicians.

Emerging Treatments and Future Directions

As alluded to above, searching for alternative treatment modalities that provide similar antiinflammatory to steroids without its negative side effect profile necessitates further avenues of innovation. Several of these emerging modalities and compounds have been highlighted in recent literature, particularly in preclinical studies examining quality of life related outcomes following SCI. This body of data has continually increased over the past several years. There is heterogeneity in experimental intervention, but locomotor functional status and pain perception were the most common outcome measures. Therapies are aimed at mitigating both acute and chronic pathological processes, many targeting the complex inflammatory cascade that contributes to worsened paralysis and hyperalgesia. We describe some of these emerging compounds below and summarize our findings in (Tables 1-3).

Study	Research Question	Significant Findings	
Study 1	Pharmacokinetic comparison of IV vs	IV 25 mg/kg dose yields [CSF] = 0.1%[Serum] and Half-life =	
	intrathecal delivery in uninjured	530 hours	

	instrumented	IV administration leads to [CSF] required to bind RGMa
Study 2	Assessment of inter-animal variability and spontaneous recovery	30-minute hemi compression model had minimal variability and closely resembles clinical setting. Spontaneous motor recovery plateaus by 4 weeks post-SCI
Study 3	Efficacy of Elezanumab in animals with 4-month-old chronic spinal cord injuries	16 weeks of chronic dosing was tolerated well without anti- drug antibody formation. 8 months post SCI no further changes in motor scores vs control
Study 4	Early intervention with IV and intrathecal Elezanumab in a T9/10 hemi compression model of SCI	Improved functional motor recovery Intrathecal dosing results in delayed CNS distribution during the acute phase.
Study 5	Effects of early (75 minutes) and delayed (24 hours) administration of IV Elezanumab on neuroplasticity	Both groups demonstrated increase white matter integrity of corticospinal tract histologically

 Table 1: Research questions and significant findings reported by Jacobson et al. regarding Elezanumab [67].

Experimental	Description	Route of	Biological	Method of SCI
compound		administration	model(s)	
Betulinic Acid	Pentacyclic triterpene acid extracted from birch bark	Intraperitoneal	Mice	Contusion T11- T12
WIN 55,212-2, ACEA, CBD, CP55,950, JWH015, PEA, PEA-OXA, and WIN 55,212-2	Synthetic analogs of endogenous cannabinoids	Highly Variable	SR: (n = 19) Rat: 13 Mice:6	Five methods used and mostly thoracic level SCI
NgR1-Fc AXER- 204	Decoy receptor for NgR1	Intrathecal/Infusions	Cynomolgus monkeys	Hemi section C5/C6
Riluzole	Glutaminergic neurotransmission inhibitor	Intrathecal/Infusions	Rats: 14 Rabbits: 2	Three methods used for injury and levels were mostly cervical and thoracic
Elezanumab	Human monoclonal antibody against RGMa	Intrathecal/Infusions	African green monkeys	T9/T10 hemi compression for five or thirty minutes
sTNFR1	Decoy receptor for TNF-a	Intrathecal	Rats	Unilateral C5 contusion
hIVIG	Human immunoglobulin G	Infusion	Rats	C7/T1 compression for one minute

 Table 2: Summary of compounds currently under investigation in reported literature. SCI = Spinal cord injury.

Experimental compound(s)	Significant findings	Proposed Mechanism of Action	
		Decreased markers of pyroptosis	
Betulinic Acid	Improved functional locomotor recovery	Increased autophagy mediated by regulation of AMK- mTOR-TFEB pathway	
WIN 55,212-2,		Acute	
ACEA, CBD,		 High CB1 receptor expression on neurons and 	
CP55,950,	Improved functional	oligodendrocytes post SCI. Agonism in period	
JWH015, PEA,	locomotor recovery and	promotes neuronal survival	
PEA-OXA, and	pain response	Chronic	
WIN 55,212-2		• Agonism on CB2 receptor expressing macrophages	
		increases IL-10 release providing analgesia	
NgR1-Fc AXER- 204	Favorable toxicology profile in non-human primates Increased functional locomotor recovery 2-3-fold increase corticospinal axon density	Decreased levels of inhibitory NgR1 promoting alters WNT/B-Catenin pathways crucial for neuronal growth.	
	Decreased lesion size Improved locomotor scores,	Blockage of sodium channels, antagonizing both NMDA and non-NMDA receptors, and GABA reuptake inhibition	
Riluzole	gait parameters, hyperalgesia, and mechanical allodynia	Leads to overall decrease in excitotoxicity secondary to pathologically high glutamate levels. Increases preservation of serotonergic and glutaminergic fibers	
Pharmacokinetic properties,Elezanumabdosage timing, and motorimprovements (table 1)		Decrease of extracellular signaling molecule RGMa which normally acts to inhibit neuronal regeneration	
sTNFR1	Consistent improvement of neurologic function Dose dependent relationship on histological findings	Attenuation of neuroinflammation secondary to increased TNF-a levels following acute SCI	
Proved hlgG is effective ifIVIGgiven within 24-hourtherapeutic window		IVIG interfered with leukocyte adhesion and rolling IVIG changed immune cell and inflammatory markers localization from circulation to spleen	

Table 3: Summary of significant findings and proposed mechanism of action of currently investigated compounds in the treatment of spinal cord injury that are reported in this review.

Betulinic Acid

Betulinic Acid (BA) is a pentacyclic triterpene acid mainly extracted from birch bark. Recent studies using a rat model of cerebral ischemic MCA stroke demonstrated reduced oxidative stress and suppression of autophagy [56,57]. Oxidative stress is a core component of the secondary injury cascade following SCI. A study done by Wu et al. specifically looked at BA's role in promoting recovery following SCI [56]. The animal model of SCI injury was created with weight-drop induced spinal contusions at the T11-T12 vertebra on mice. Daily intraperitoneal injections of 20 mg/kg of BA were given for three days following SCI. Functional behavioral assessment, histological staining, and lab studies mentioned before were analyzed comparing to a control. BA treated animals had less glial scarring and increased SYN-positive synapses on ventral motor horns.

Pyroptosis is an inflammatory form of programmed cell death found to be decreased with BA administration based on inflammatory cascade markers. BA decreased levels of ASC, GSDMD, Capsase-1, NLRP3, IL-1B and IL-18 compared with the control group suggesting it plays a role in reduction of pyroptosis. To assess BA's effect on autophagy LC3II, Beclin1, Vps34, CTSD, and p62 protein levels were assessed. These proteins describe autophagosomal markers. BA increased levels of all proteins indicating increased autophagy, the only substrate lowered was p62, an auto-phagocytic substrate protein (further suggesting autophagy up-regulation). Additionally, the AMPK-mTOR-TFEB activity was investigated. TFEB, known as the activator of autophagy and augments mitophagy. There is controversy regarding autophagy being beneficial or harmful in the context of SCI, but this paper found improved functional locomotor recovery in an animal model along with data to support the mechanism of action BA exhibits these effects [56].

Cannabinoids

Historically, federal restrictions have limited research on cannabinoids (CBs) and related compounds in SCI. Aside from being the psychoactive constituent of marijuana, CB exist as endogenous compounds and modulation of these receptors may have therapeutic potential in dealing with chronic pain and affective disorders associated with SCI. Prior evidence exists supporting CB's role in the CNS injury cascade. In a traumatic brain injury mouse model an endogenous cannabinoid, Arachidonoyl Glycerol (2-AG), may have a neuroprotective role. Levels were significantly elevated after brain injury and administration of synthetic 2-AG reduced brain edema and improved infarct volume and hippocampal death. 2-AG benefit was further evidenced by a dose dependent attenuation using SR-131761A, a CB1 receptor antagonist [58]. This neuroprotective mechanism is attributed to decreased excitotoxicity secondary to CBs NMDA receptor blockade properties. 2-AG additionally prevents formation of TNF-alpha and ROS.

A recent systemic review assessed the impact cannabinoid agonists (WIN 55,212-2, ACEA, CBD, CP55,950, JWH015, PEA, PEA-OXA, and WIN 55,212-2) and antagonists (AM630) have on neurobehavioral outcomes in preclinical models of SCI. Animal models of injury included compression, contusion, ischemia-reperfusion, cryogenic, and transection (partial). Agonists demonstrated statistically

significant improvement on locomotor function in 9/10 studies and improve pain outcomes in 6/6 studies [59]. CBs were theorized by authors to act in a biphasic manor. Acutely (within the first week) after injury CBs promotes neuronal survival. Oligodendrocytes and neurons have increased CB1 receptors acutely after injury, during a time period essential for neuronal survival. Chronically (two to three weeks post SCI) CBs increase IL-10 release from CB2 expressing macrophages, which is the proposed mechanism for analgesia [58].

Nogo receptor decoy

Notoginsenoside Receptor 1 (NgR1) is an active compound isolated from *Panax notoginseng* used in traditional medicine acting as an antioxidant. There are several extracellular molecules that inhibit synaptic sprouting and neuronal plasticity. Nogo-A appears to be the most important of these inhibitory ligands and this soluble decoy receptor binds to Nogo-A, encouraging anatomical growth and regeneration of neurons. NgR1 has been demonstrated in prior studies to alleviate glutamate induced oxidative stress, apoptosis, and mitochondrial dysfunction via SIRT1 activation of the WNT/B-Catenin pathways [60,61].

A recent study done on cynomolgus monkeys and rats investigated a soluble decoy receptor for a myelin-associated inhibitor NgR1. The soluble decoy NgR1-Fc AXER-204 has been promoted recovery in a series of preclinical rodent models, but this most recent study proved safety and efficacy in a non-human primate. Results showed no toxicology or safety concerns⁶¹. The SCI model used was a C5/C6 right hemi section followed by one treatment arm receiving chronic intrathecal and IV NgR1-Fc every other day. Histological analysis demonstrated a 250% increase in corticospinal axon density in the cervical cord below the level of the injury when compared with control. Behavioral analysis showed increase in affected right arm use from 6% in the control to 17% in the experimental group.

Riluzole

Riluzole is a glutamatergic neurotransmission inhibitor with survival benefit in amyotrophic lateral sclerosis (ALS). Riluzole's mechanisms of action is not completely understood. It is theorized the impact is secondary to a multifactorial process altering synaptic concentrations of excitatory amino acids. It is proposed to do so by blockage of sodium channels, antagonizing both NMDA and non-NMDA receptors, and GABA reuptake inhibition [62]. This benzothiazole class small molecule blocks excessive glutamate release from motor neurons. Decreased glutamate slows the excitotoxic cascade known to cause neuronal death [63].

There is a body of evidence demonstrating neuroprotective, anti-ischemic, and anti-epileptic properties of riluzole [64] . In a recent systematic review on the neurobehavioral outcomes in preclinical models of nontraumatic and traumatic SCI, sixteen studies were analyzed with a variety of SCI models including traumatic, degenerative, and ischemic. Animal models used were mostly rat (n=14) and some rabbit studies (n=2). Experimental groups received an assessment of post-injury locomotor, pain, and behavioral outcomes. Results showed significant impact on locomotor scores, gait parameters, hyperalgesia, and mechanical allodynia. Notably, it was found that lower doses (0.8 or 2.5 mg/kg) failed to demonstrate improvements in neuropathic pain. The review also hypothesized that the ventral

posterolateral nucleus of the thalamus may be an important target based off a dose response gradient observed on intracerebroventricular injection of riluzole. Although histological and behavioral benefits were seen, there was no alteration of lesion size nor scarring pattern [64]. The systematic review proposed additional explanations for outcome improvements. They proposed improvements could be secondary to increased survival of serotonergic and glutamatergic fibers involved in fine motor control and increased neuron counts in red, reticular and vestibular nucleus. This study suggests that riluzole may mitigate the oxidative damage caused by reperfusion following decompressive surgery. Direct comparison of riluzole to other compounds will be reviewed below.

Riluzole, hypothermia, and glibenclamide direct comparison

Another study compared riluzole head-to-head with two other treatment modalities showing preclinical promise, hypothermia and glibenclamide. These three treatments were specifically identified to interfere with progressive hemorrhagic necrosis (PHN), which is irreversible conversion of healthy tissue secondary to advancing microvascular dysfunction. With existing preclinical data coming from a variety of labs using differing SCI injury models and outcome assessment, this study provided valuable direct therapeutic comparison under a controlled environment. Compounds were delivered four hours after trauma using a unilateral impact injury model at the C7 cord producing isolated ipsilateral hemorrhage. Riluzole was dosed at 8 mg/kg IP twice daily, glibenclamide was dosed 10 μ g/kg IP loading dose followed by a one-week long subcutaneous pump delivery of 400 ng/hour, and systemic moderate hypothermia (epidural temperature 33.0 C +/- 0.3) was induced for four hours under anesthesia.

Direct comparison revealed favorable results in all three compounds compared to control. The hypothermia and glibenclamide treatments performed in a similar manor, both outperforming riluzole treated rats in the first two weeks. Prior to day seven riluzole also showed a higher degree of autonomic dysfunction compared with other treatments (ptosis, heart rate, and temperature changes). After six weeks results between the compounds were identical and lesion volume assessed at the time was smaller in all three groups. Largest reduction in lesion volume was noted in the glibenclamide treatment followed by hypothermia and riluzole, respectively. After injury all groups showed atrophy of the spinal groups rostral to the lesion except riluzole. Of the three, riluzole showed higher mortality rates attributed to its unfavorable therapeutic index. Final comparison results concluded that all are strong candidates for translation into clinical trials and that systemic hypothermia and glibenclamide may have a greater efficacy and safety profile compared to riluzole [65].

Elezanumab

Repulsive guidance molecule A (RGMa) is a molecule important for the processes of cell migration, differentiation, and apoptosis of different organs [66]. Several studies have been done over the years as early as 2006 investigating its potential in SCI. This molecule modulates axonal regeneration following SCI. RGMa binds to neogenin 1 (Neo1) and serves as a coreceptor for bone morphogenic protein (BMP) family of receptors [67]. When RGMa binds to Neo1 it triggers a proteolytic sequence that structurally changes actin cytoskeletons that has been implicated in axonal pathfinding and neuronal migration [68]. RMGa is upregulated following spinal cord injury and inhibits axonal growth and remyelination.

Elezanumab is a human anti-RGMa monoclonal antibody that decreases levels of RGMa, encouraging neuronal recovery.

Recent studies have explored Elezanumab impact on functional neurological recovery in the clinical and preclinical context. The antibody is currently being investigated in Phase II clinical trials for multiple sclerosis, acute spinal cord injury, and acute ischemic stroke. In a mice model of noise induced cochlear damage, RGMa antibody improved synaptic regeneration [66].

A recent series of five studies was conducted by Jacobson [67] and colleagues on non-human primates. These studies served to validate functional recovery and histological evidence of benefits while further investigating pharmacokinetic properties of the antibody (Table 1). Overall, the findings demonstrated several months of intravenous (IV) Elezanumab provided neuroprotective and neuroplastic effects alongside modest improvements in lower limb function. All of the studies were done on African green monkeys. SCI was simulated using a T9/T10 hemi compression model for either 5 or 30 minutes to evaluate efficacy of early intervention. This series of studies provides crucial data necessary before progressing with additional clinical trials. IV administration is a less invasive method of delivery that demonstrates advantages to intrathecal delivery (Study 1). Prior published studies investigated Elezanumab use prophylactically or immediately following SCI. This study provided data on delayed treatment, yielding practical information for real life clinical practice where intervention is often delayed (Study 5).

Soluble TNF-a receptor 1

TNF-a is known to be one of the most potent pro-inflammatory cytokines and is elevated following acute SCI [69,70]. Large scale-data driven discovery technique was used to extract syndromic information five preclinical studies aiming to link biological and neurobehavioral outcomes. Variables were obtained from five blinded preclinical neuroinflammation trials performed on rats in a single lab over 10 years. A unique machine learning approach was taken to analyze consistent multidimensional syndromic benefit. The technical aspects of this analytical technique are beyond the scope of this paper, but included topographical data analysis (TDA) and principal component analysis (PCA) [69]. TDA evaluated minocycline, ciclopirox, and methylprednisolone failed to show consistent behavioral benefit under multivariate analysis. Human recombinant soluble TNF receptor 1 (sTNFaR1) was the only compound demonstrating consistent benefit on outcomes of combined variables. PCA analysis provided quantification of the drugs effect and yielded a dose dependent improvement of aggregate syndromic metrics. This dose dependent improvement was created using a limited dataset of histopathological outcome measures.

The data obtained on sTNFaR1 used a C5 unilateral cervical contusion model. Immediately following the contusion, 10 µL of sTNFaR1 was delivered intrathecally over 5 minutes. A series of new experiments revealed that a 90-minute delayed bolus dose to the contusion reduced expression of neuroinflammatory markers and consistently improved neurological function over a six-week period [69]. This study highlights sTNFaR1's therapeutic potential and further clarifies optimal responses to

different administration windows. Furthermore, it is proof of concept that multivariate analysis serves as a powerful tool to streamline evaluation of preclinical data and choose promising targets for continued evaluation.

Intravenous Immunoglobulin

Delayed administration of high dose human immunoglobulin G (hIgG) was investigated by Chio et al. using an animal SCI model on Wistar rats [71]. Prior studies conducted by Chio et al. demonstrated hIgG's effectiveness 15 minutes post SCI. The most recent study evaluated differential effectiveness with delayed administration. A single bolus of 2 g/Kg was administered through a peripheral vein. Administration at 15 minutes post SCI delay was used as the control with other experimental groups receiving hIgG at one hour and four hours. The SCI model used was a compressive force delivered at the C7/T1 level for one minute. At 24 hours and 8 weeks following SCI molecular, histological, and neurobehavioral analyses were undertaken.

Delayed administration of high dose human immunoglobulin G (hIgG) was investigated by Chio et al. using an animal SCI model on Wistar rats [71]. Prior studies conducted by Chio et al. demonstrated hIgG's effectiveness 15 minutes post SCI. The most recent study evaluated differential effectiveness with delayed administration. A single bolus of 2 g/Kg was administered through a peripheral vein. Administration at 15 minutes post SCI delay was used as the control with other experimental groups receiving hIgG at one hour and four hours. The SCI model used was a compressive force delivered at the C7/T1 level for one minute. At 24 hours and 8 weeks following SCI molecular, histological, and neurobehavioral analyses were undertaken.

Conclusion

Traumatic spinal cord injury represents a significant neurological insult with high morbidity and mortality. It is associated with devastating acute and long-term neurological outcomes with limited avenues for meaningful intervention. SCI often occurs as a result of blunt force trauma and a resulting inflammatory cascade due to secondarily compromised vascular supply, pro-inflammatory mediators, and neuronal dysfunction due to changes in the microenvironment. In the acute phase of injury, neurological impairment should be assessed as quickly as is reasonably possible. Clinical tools such as the AIS scale can assess neurological impairment and provide some prognostic information. Although its prognostic ability has been validated in several studies, it has not yet been proven useful in informing immediate clinical decisions regarding medical and surgical intervention.

Outside of medical management involving adequate hydration and hemodynamic support, surgical decompression has been the mainstay of treatment to relieve pressure from the spinal cord as a result of edema or other surrounding tissue damage. The notion of "time is spine" has been a predominant theme, with studies showing benefit in surgical intervention within 24 hours of injury. However, there remains substantial contention in regards to the optimal timeframe for surgical intervention. Current and future studies will be required to fully understand the best timing for surgical intervention and help stratify patients that stand to benefit from these invasive procedures.

Despite appropriate surgical and medical intervention patient's often do not regain meaningful neurological function following SCI. Emerging treatment modalities have offered some hope however in pre-clinical studies. Organic compounds, small molecules, and antibodies have shown considerable promise in modifying the SCI cellular microenvironment in favor of more positive outcomes. These experiments have mainly been carried out in murine and non-human primate models with varying success. More research will need to be conducted to better assess the efficacy and safety profile of these emerging treatments with the hope of advancing more of these novel interventions to human clinical trials.

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