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COMMENTARY

MMP-9 and -12 inhibition in spinal cord injury restores function

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Spinal cord injury (SCI) is a devastating condition causing permanent disability and death. There are approximately 200 000 to 1.263 million new cases of SCI each year with the biggest causes being motor vehicle accidents, falls and interpersonal violence. The clinical outcomes of SCI depend on the severity and location of the lesion and may include partial or complete loss of sensory and/or motor function below the level of injury. However, there are no fully restorative treatments for SCI and current treatments only offer symptomatic relief but do not target the underlying pathophysiology. A recent study by Ahmed et al. in *Clinical and Translational Medicine*[1] shows that inhibiting the early rise in matrix metalloproteases-9 (MMP-9) and -12 (MMP-12) using a clinically relevant and specific inhibitor, AZD1236, attenuates oedema, prevents blood-spinal cord barrier (BSCB) breakdown, attenuates neuropathic pain, promotes axon regeneration and thus recovery of sensory and locomotor function. Thus, AZD1236 represents a first-in-class drug that has the potential to treat the key SCI pathophysiology, offering a real solution for patients with SCI.

MMPs are a family of zinc-dependent proteases which target chemokines, cytokines, cell surface receptors and a host of structural extracellular matrix proteins. In SCI, MMPs degrade components of the basal lamina, leading to disruption of the BSCB, increased oxidative stress, leukocyte infiltration, progressive neuroinflammatory response, myelin degradation, haemorrhagic transformation, neuronal death and neuropathic pain.[2] MMP-9 is a 92 kDa gelatinase and its levels peak within 1 day after SCI and is detected in glia, macrophages, neutrophils and vascular elements. Excessive MMP-9 contributes to disruption of the BSCB, excitotoxicity, leukocyte influx, apoptosis, mitochondrial dysfunction, demyelination and astrogliosis. MMP-12 is a 54 kDa elastinolytic protease and is mainly expressed by macrophages. MMP-12 levels peak at 5 days after SCI and contribute to the inflammatory response, acute oedema and the development of secondary injury responses.

Genetic knockout of MMP-9 and MMP-12 demonstrated improved functional recovery, reduced BSCB breakdown and reduced neuropathic and inflammatory pain.[3] These studies provided strong evidence that short-term blockade of MMP-9 and -12 may have beneficial neuroprotective effects, without perturbing the requirement of these enzymes during the healing phases in the spinal cord. Many biological tool inhibitors of MMPs have been developed and tested in animal models including GM6001, Inhibitor I, SB-3CT, lipitor, fluoxetine and sulforaphane.[4] These inhibitors showed promise in animal models, but MMP inhibitors suitable for clinical use have never been tested in SCI. This may in part be due to the mechanistic risk of musculoskeletal side-effects which have hampered development of MMP inhibition as a mechanism in the

clinic, severely limiting continuous dosing regimens. This side-effect is particularly evident with broad-spectrum MMP inhibitors. AZD1236 however, is a potent, orally bioavailable, reversible and specific inhibitor of human MMP-9 (IC_{50} = 4.5 nM) and MMP-12 (IC_{50} = 6.1 nM), with 10- to 15-fold selectivity against MMP-2 (IC_{50} = 69 nM) and MMP-13 (IC_{50} = 97 nM), and >350-fold selectivity against other members of the MMP and a disintegrin and metalloproteinase (ADAM) family. Safety studies support continuous dosing for up to 6 weeks in humans; attributable to the increased selectivity of the compound for MMP-9 and -12 relative to other MMP family members. AZD1236 has been used in Phase 2 clinical trials in chronic obstructive pulmonary disease (COPD) by AstraZeneca, where it was found to be safe and well tolerated following 6 weeks continuous dosing.[5,6]

In the study by Ahmed et al.[1], they used rodent preclinical models of SCI,[7] to determine if short-term inhibition of MMP-9 and MMP-12 (during the period immediately post-SCI when these enzymes are excessively upregulated and can cross-over into the injured cord via the 'leaky' BSCB), using AZD1236 attenuated SCI-induced oedema and secondary damage to the spinal cord, and, thus, prevented the decline in sensory and locomotor function. MMP-9 levels and activity in the spinal cord and the cerebrospinal fluid (CSF) peaked within the first 24 h, whilst MMP-12 peaked 5 days post-SCI. Both oral and intra-thecal delivery of AZD1236 significantly attenuated MMP-9 and MMP-12 activity in both serum and CSF, and completely suppressed the SCI-induced rise in water content in the spinal cord; an effect that was directly related to inhibition of both MMP-9 and MMP-12. Blocking oedema is correlated with neurological outcomes and correlates with improved clinical outcomes after SCI and if left unchecked can lead to further damage and death, posing a significant challenge to neurosurgeons. In the CNS, aquaporin-4 (AQP4) is the major water channel protein and regulates BSCB permeability during spinal cord oedema and pharmacological inhibitors of oedema, such as melatonin or AQP4 relocalisation, attenuate oedema after SCI.[8] It is likely that AZD1236 also attenuated AQP4 levels but this has not yet been studied.

Ahmed et al.[1] also showed that measures of proinflammatory pain markers, behavioural responses to pain, BSCB breakdown and scarring at the lesion site were also suppressed by inhibition of MMP-9 and MMP-12. Suppressed macrophage activation at the lesion site and resident microglial activation were also observed, probably related to reduced BSCB breakdown and, hence, an overall reduction in damage to the spinal cord. Furthermore, inhibition of MMP-9 and MMP-12 enhanced axon regeneration and increased spared fibres above and below the lesion site contributing to enhanced electrophysiological,

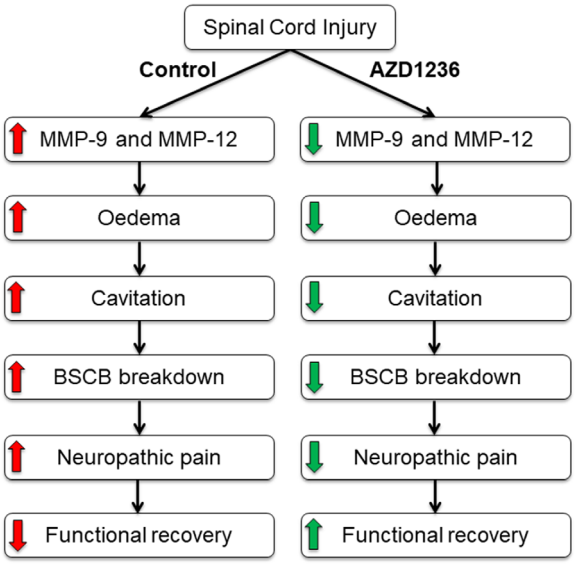

FIGURE 1 AZD1236 has multiple benefits after spinal cord injury (SCI). AZD1236 suppresses MMP-9 and MMP-12 levels and activity, spinal cord oedema, cavitation, BSCB breakdown, neuropathic pain and improved functional recovery. AZD1236 is, therefore, a potential first-in-class drug to promote improved outcomes after SCI

sensory and locomotor function recovery. For example, AZD1236-treated rats recovered sensory and locomotor function such that by 3 weeks after SCI, they appeared no different to sham-treated controls, whilst SCI animals still showed signficant functional deficits after 6 weeks.

In conclusion, specific short-term inhibition of MMP-9 and MMP-12 with AZD1236 has profound effects on the extent of secondary damage to the spinal cord and the potential for recovery and represents a promising first-in-class reparative drug for SCI (Figure 1).

CONFLICT OF INTEREST

ZA is an inventor on a patent related to this work.

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