Flubendazole antimitotic therapy for spinal cord injury

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Traumatic SCI significantly causes mitotic cell proliferation of B cells, astrogcytes, and fibrotic cells, which leads to inflammation, astroglial/fibrotic scar formation, autoimmunity, myelin/axon damage, inhibition of axonal regeneration, locomotor deficits and pain. However, no approved anti-B cell or anti-scarring products are available for SCI indications. Flubendazole (FluBZ) is a novel tubulin-binding antimitotic agent that is known to inhibit tubulin polymerization by binding a site on tubulin similar to colchicine but distinct from that of Vinca alkaloids. FluBZ has been widely used in the treatment of intestinal and neural parasites in human and can be safely administered long term up to two years in human without side effects. Here we show that FluBZ anti-mitotic therapy reduces proliferating signaling pathways of B cells, astrocytes, and fibroblasts and demonstrates potent anti-autoimmunity, anti-inflammation, anti-nociception, and inhibition of astroglial/fibrotic scaring after SCI. Intraperitoneal (IP) injection with 5 and 10 mg/kg/day (n=10/group) of FluBZ to Sprague-Dawley rats for 2 or 4 weeks started at 3 or 5 hrs post-SCI (180 kdyn) at T10. These FluBZ treatments resulted in improved locomotor function (BBB scores and kinematic analysis) 7 weeks after SCI and reduced pain behaviors 4 weeks after excitotoxic SCI compared to vehicle-treated controls (n=9/group). FluBZ IP treatment also improved total tissue sparing, white matter sparing, and gray matter sparing at 7 weeks after SCI. Mechanistic studies revealed that FluBZ reduced splenic population of CD45RA-positive B cells and spinal GFAP-positive astrocytes as well as PDGFR-beta-positive fibrotic cells at 4 or 7 weeks post-injury and suppressed production of antibody IgG at lesion site post-injury. Moreover, we found that FluBZ inhibited mitotic signaling activation of mitogen-activated protein kinase pERK1/2 and mitotic cell cycle protein activator cyclin B1 at lesion site 4 weeks post-injury. Cyclin B1 is well known to be an important mitotic cell cycle protein at G2/M phase for mitotic cell activation and proliferation. ERK1/2 is a marker of pain and part of the cell cycle machinery and its activation can accelerate the cell cycle progression at G2/M transition. In conclusion, our results demonstrate that FluBZ antimitotic therapy inhibiting proliferation of B cells, astrocytes, and fibrotic cells as well as mitotic signaling is a valid therapeutic strategy for treating paralysis and pain following SCI.