Alcohol abuse is associated with dysfunction of glutamatergic system along with other neurotransmitter systems in mammalian central nervous system. Studies have shown that both behavioral effects of acutely administered alcohol and neuroadaptation associated with chronic ethanol intake are mediated by glutamatergic neurotransmission in key regions of brain reward circuitry. Extracellular glutamate level has been reported to be elevated following alcohol consumption. The role of several glutamate transporters in restoring glutamate homeostasis has been well established. Among these, glutamate transporter 1 (GLT1) and cystine-glutamate antiporter (xCT) are key players in regulating extracellular glutamate levels. Previous studies from our lab have reported that ceftriaxone, a β-lactam antibiotic known to upregulate GLT1, attenuated ethanol consumption in alcohol preferring (P) rats in chronic ethanol-drinking paradigm. This effect was associated in part with GLT1 upregulation in central brain reward regions. In the present study, we investigated the short and long lasting effects of MS-153, GLT1 activator, on ethanol intake and glutamate transporters’ expression in male P rats. We further examined the effects of MS-153 and Augmentin combination on ethanol consumption, body weight and water intake in P rats. P rats were exposed to five weeks of continuous free-choice ethanol drinking paradigm. On the first day of week 6, P rats were injected intraperitoneally with MS-153 (50 mg/kg), or a combination of MS-153 (50 mg/kg) and Augmentin (100 mg/kg), or vehicle for five consecutive days. Interestingly, we found a significant reduction in ethanol intake in P rats treated with MS-153 starting 24 hours after the first injection, which lasted up to ten days after the last injection as compared to vehicle-treated animals. This long lasting effect on ethanol consumption was associated with significant upregulation of GLT1 levels in the nucleus accumbens (NAc) but not in the prefrontal cortex (PFC). Additionally, one day after the last MS-153 injection, xCT levels were significantly upregulated in amygdala and hippocampus. Furthermore, treatment with combination of MS-153 and augmentin resulted in reduction of ethanol consumption as compared to vehicle-treated rats. Our study demonstrates that modulating GLT1 and xCT expression may be a promising therapeutic target for treating alcohol dependence.