INTRODUCTION:
Controversy exists regarding the value of anti-tumor necrosis factor (TNF-α) therapy in the treatment of peripheral nerve injury. Anti-TNF-α agents are reported to inhibit injury induced neuropathic pain by down-regulating Nav 1.3 and Nav1.8. On the other hand, there is a suspicion that they induce demyelination especially when applied to those with preexisting demyelinating neuropathies. Therefore, multiple sclerosis and optic neuritis are listed as contraindications without concrete scientific evidence. The purpose of this study is to evaluate the effect of TNF-α inhibition on functional recovery after nerve injury.

MATERIALS and METHODS:
Animal model: Adult male Lewis rats (bodyweight approximately 250 g each) were anesthetized with 5% pentobarbital sodium at a dose of 40-50 mg/kg. Rats were divided into 3 groups (each group n=12) experimental, sham, and control groups. Half of the rats in each group were sacrificed after 3 weeks and the remaining rats in each group were evaluated behavior until 5 weeks. In the experimental group, 6mg/kg of etanercept was administered intraperitoneally, and then the right sciatic nerve was exposed and subjected to crush injury using a Sugita clip with 1.5N force for 5 minutes. The rats of the control group received vehicle and underwent the same procedure. The rats of sham group only had a skin incision. Motor recovery was monitored every week up to 5 weeks after surgery by calculating sciatic functional index (SFI) using an automated quantitative gait analysis system, the CatWalk. In addition to motor function, mechanical and thermal hypersensitivity were measured using von Frey test and plantar tests according to the Hargreaves' method, respectively.

After the final evaluation, the rats were anesthetized and compound muscle action potential (CMAP) was measured from the tibialis anterior muscle (TA). Then the rats were sacrificed and the TA, gastrocnemius muscle (GC), L5 dorsal root ganglia, and sciatic nerve were harvested bilaterally. Wet muscle weights were measured and expressed as a percentage of total body weight. The expression level of Nav1.3 and Nav 1.8 at DRG were measured using real time RT-PCR.

RESULTS:
The latency of the control group was significantly longer than that of the etanercept group 3 and 5 weeks after surgery (Figure 1). The control group showed significantly lower percentage of wet muscle weight of the tibialis anterior muscle (TA) and L5 dorsal root ganglia, and sciatic nerve were harvested bilaterally. Wet muscle weights were measured and expressed as a percentage of total body weight. The expression level of Nav 1.3 and Nav 1.8 at DRG were measured using real time RT-PCR.

DISCUSSION:
Previous studies have confirmed that TNF-α expression transiently but strongly upregulated in the distal stamp following nerve injury and plays significant roles in the initiation and progression of wallerian degeneration. Sawada studied the spatiotemporal expression pattern of TNF-α and found that it peaked at 3 days after injury and then started to decrease down to the control level by day 7, suggesting its role in the initiation and progression of myelin degradation. Contrary to the above mentioned suspicion, previous studies showed that neutralizing antibody against TNF-α ameliorate inflammatory demyelination in animal models. In addition, knockout mouse lacking TNF-α showed impaired macrophage infiltration and marked preservation after induction of wallerian degeneration. This study clearly demonstrated that anti-TNF-α antibody not only improves functional recovery after crush injury but also ameliorates both thermal and mechanical hyperalgesia. In contrast to He’s study, expression of Nav 1.3 and 1.8 did not elevate in DRG in our model. This may partly be due to the difference in animal model, however, our unpublished study using CRPS model also could not confirm He’s finding. Therefore, we think that mechanisms other than upregulation of voltage gated sodium channel are responsible for TNF-α induced hyperalgesia.

SIGNIFICANCE: Anti-TNF-α for the peripheral nerve injury is still controversial. This study revealed the neuroprotective effect of the sciatic nerve.

REFERENCES: