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# The c-Abl inhibitor, nilotinib, as a potential therapeutic agent for chronic cerebellar ataxia

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ABSTRACT

Nilotinib is a potent inhibitor of tyrosine kinase BCR-ABL that penetrates the blood–brain barrier. To evaluate the effect of nilotinib in chronic cerebellar ataxia, twelve patients with chronic cerebellar ataxia nonresponsive to other treatment options (modified Rankin scale [mRS] scores: > 2) and received nilotinib therapy (daily doses: 150–300 mg) for > 4 (range 5–16) weeks were reviewed. At follow-up, improved mRS scores were found in 7/12 (58.3%) patients and favorable mRS scores (≤ 2) were found in 6/12 (50.0%) patients. No severe adverse event was observed. Atrophy in the cerebellar vermis appeared to be negatively associated with favorable outcomes.

## 1. Introduction

Chronic cerebellar ataxia (CA) is a neurological disorder that leads to the progressive deterioration of functions involving motor coordination and posture maintenance, resulting in a substantial limitation in patients' quality of life (Abele et al., 2002; Brusse et al., 2007; Kim and Cho, 2015; Koeppen, 2005; Schöls et al., 2004). Degeneration of the Purkinje cells (PC) in the cerebellum, ion channel dysfunction, and dysregulation of synaptic neurotransmitters have been suggested as common pathophysiological processes underlying chronic CA (Koeppen, 2005). Genetic, degenerative, and autoimmune causes have been recognized as the major etiologies of CA; however, a considerable portion of patients remains classified as idiopathic (Abele et al., 2002, Brusse et al., 2007, Kim and Cho, 2015). Attempts have been made to cure the underlying etiologies after the identification of potentially treatable causes, such as immunotherapy for autoantibody-associated cerebellar degeneration (Shams'ili et al., 2003). However, currently established treatment strategies for chronic CA remain at the level of symptom alleviation (Bürk et al., 1996, Brusse et al., 2007).

Nilotinib (AMN107; Tasigna) is a recently developed inhibitor of non-receptor tyrosine kinase BCR-ABL (c-Abl) (Saglio et al., 2010). Because nilotinib has higher potency and selectivity for c-Abl than imatinib, it has been established as an effective second-line agent for treating imatinib refractory chronic myeloid leukemia (Saglio et al., 2010). Activated c-Abl tyrosine kinases disturb the clearance of intranuclear/cytoplasmic aggregation of abnormal proteins via autophagy and are involved in apoptotic processes in response to various cellular stresses. Therefore, the efficacy of c-Abl inhibitors has been investigated in various central nervous system (CNS) degenerative diseases with relevant pathomechanisms such as amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and Niemann–Pick disease (Hebron et al., 2013; Imam et al., 2013; Karuppagounder et al., 2014; Katsumata et al., 2012; Vázquez et al., 2012). Furthermore, because nilotinib effectively penetrates the blood–brain barrier, nilotinib has been established as effective in treating preclinical models of Alzheimer's disease and Parkinson's disease via activating the parkin ubiquitination, interaction with Beclin-1, and promoting autophagic clearance (Hebron et al., 2013; Lonskaya et al., 2013a; Lonskaya et al., 2013b;

*Abbreviations:* CA, cerebellar ataxia; PC, Purkinje cells; SCA, spinocerebellar ataxia; DRPLA, dentatorubral–pallidoluysian atrophy; MSA-C, multiple system atrophy-cerebellar type; MCP, middle cerebellar peduncles; CTCAE, Common Terminology Criteria for Adverse Events; NO, nitric oxide; TDP-43, TAR DNA-binding protein 43

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Lonskaya et al., 2014), and also being able to improve the symptoms of patients with Parkinson's disease with a favorable safety profile (Pagan et al., 2016). Considering that chronic CA caused by various etiologies commonly involves long-term PC degeneration and that c-Abl is also widely associated with dysregulated synaptic function or the plasticity of PC, nilotinib could be effective in treating CA (Canepari and Ogden, 2003; Glover et al., 2000; Heyburn et al., 2016; Koeppen, 2005).

In this study, we report 12 cases of chronic CA treated with nilotinib, including an analysis of the magnetic resonance imaging (MRI) findings, clinical profiles, and the outcomes of the patients. Furthermore, we evaluated the factors potentially associated with the responsiveness to nilotinib treatment.

## 2. Materials and methods

### 2.1. Study population

We retrospectively analyzed 12 patients who were diagnosed with chronic CA, received daily oral nilotinib therapy for > 4 weeks, and were followed up at our single tertiary hospital. The patients showed chronic (≥ 6 months) ataxic symptoms that significantly limited their daily routine activities [modified Rankin scale (mRS) scores of > 2] and were nonresponsive to other treatment options. The patients themselves and their caregivers decided to start nilotinib treatment after being comprehensively informed about the potential efficacy, adverse effects, and cost of nilotinib treatment by their referring physicians. Before nilotinib administration, each patient was assessed for chronic disorders involving the liver, heart, or kidney and underwent a full laboratory workup, including complete blood count, serum electrolytes, liver enzymes, and antibodies for chronic hepatitis viruses as well as electrocardiography (Pagan et al., 2016, Saglio et al., 2010). The design of this study was reviewed and approved by the institutional review board of Seoul National University Hospital. Because the patient information was anonymized and de-identified prior to our analysis, the requirement for informed consent was waived.

### 2.2. Acquisition of clinical data

A battery of investigations to determine the relevant etiology was performed at the time of the initial diagnosis of chronic CA. This included cerebrospinal fluid (CSF) examination, screening for autoantibodies associated with autoimmune diseases/paraneoplastic neurological syndromes using their serum/CSF samples (Iizuka et al., 2016, Lee and Lee, 2016, Lee et al., 2016, Shams'ili et al., 2003, Smitt et al., 2000), and surveillance for the most common genetic mutations that cause CA, which include spinocerebellar ataxia (SCA) 1, 2, 3, 6, 7, and 17 and dentatorubral–pallidoluysian atrophy (DRPLA) (Kim and Cho, 2015, Schöls et al., 2004). The presence of autonomic/sphincter signs or symptoms, cognitive dysfunction, and pyramidal signs were also evaluated (Abele et al., 2002, Brusse et al., 2007, Gilman et al., 2008). The results of the investigations were used to classify the etiologies of chronic CA into genetic, autoimmune, degenerative [multiple system atrophy, cerebellar type (MSA-C)], and idiopathic (Abele et al., 2002, Brusse et al., 2007, Lee and Lee, 2016). Medications used to modify the disease course (such as immunotherapies for autoimmune etiologies) or to alleviate symptoms were also reviewed.

### 2.3. Acquisition of MRI data

The brain MR images obtained prior to nilotinib treatment using a 1.5/3.0-Tesla imaging unit were analyzed. Atrophic changes involving the cerebellar vermis, cerebellar hemispheres, pons, middle cerebellar peduncles (MCPs), and cerebral hemispheres were evaluated using sagittal T1-weighted, axial T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images. Widening of the prepontine cistern, thinning of the pontine brainstem, and sparsity of the vermian structures were evaluated at the midline section of the T1 sagittal images. Widening of the sulci in the cerebellar and cerebral hemispheres and thinning of the MCP and pons were evaluated using axial T2-weighted and FLAIR images (Bürk et al., 1996; Tavani et al., 2003). The severity of the atrophic changes was categorized into none, mild, moderate, and severe by a neurologist (WJL, 5 years of experience) and a radiologist (YJR, 5 years of experience) in consensus, and both were blinded to all clinical information. Moderate or severe atrophic changes were regarded as significant.

### 2.4. Outcome analysis

The patients were followed up 2, 4, and 4–8 weeks after the initiation of treatment to monitor their responsiveness and adverse drug reactions to nilotinib. At each follow-up appointment, patients underwent complete blood count, serum electrolyte, and liver enzymes testing as well as electrocardiography; in addition, they were assessed for the onset of any adverse symptoms (Pagan et al., 2016, Saglio et al., 2010). Any adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE v4.3). The medication dose was adjusted by the clinician when needed based on the patients' responsiveness and tolerance to the drug. Changes in functional status were evaluated using mRS scores (0–6) at baseline and at the last follow-up based on both the review of medical records and a retrospective telephone call to the patient and their primary caregivers. A favorable outcome of nilotinib treatment was defined as achieving a mRS score of ≤ 2 after drug initiation. Responders were also asked when they first noticed an improvement in their functional status and whether the drug effect was progressive and stable or if it decreased during the follow-up period.

### 2.5. Statistical analysis

SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Data are reported as numbers (percentage), mean ± standard deviations, or median (range). The Wilcoxon signed-rank test was used to evaluate the mRS score changes between the baseline and follow-up. Mann–Whitney *U* tests and Fisher's exact tests were used to analyze the associations of clinical and MRI factors with the clinical responsiveness to nilotinib treatment. *P* values < 0.05 were considered to indicate statistical significance.

## 3. Results

Twelve patients with chronic CA (four males and eight females) with a mean age of 54.4 ± 11.4 (range 31–74) years were included. According to their underlying etiologies, three patients were classified with autoimmune (associated with anti-Yo, anti-amphiphysin, and anti-collapsin response mediator protein-5 antibodies), three patients with degenerative (all with probable MSA-C) (Gilman et al., 2008), three with genetic (two with SCA2 and one with SCA7), and three with idiopathic CA. Among the patients, gait ataxia was the most prevalent (12/12, 100.0%) and dominant symptom, followed by dysarthria (10/12, 83.3%) and dizziness (8/12, 66.7%, see Table 1). In the analysis of the pre-treatment MR images, 6/10 (60.0%) patients had a significant atrophy at cerebellar vermis, 6/11 (54.5%) patients at cerebellar hemispheres, 4/11 (36.4%) patients at pons, and 3/11 (27.3%) patients at MCP (Table 2). Nilotinib was initiated with a mean delay of 3.6 ± 2.3 (range 0.75–9) years from the onset of disease. Before nilotinib administration, three patients with autoimmune CA received intravenous administrations of immunoglobulin, rituximab, tocilizumab, and interleukin − 2 in consecutive order, none of which consistently improved their symptoms. Upon comprehensive cancer workup and follow-up for the patients with autoimmune CA (Lee and Lee, 2016), two patients (patients 2 and 3) were positive with a thyroid nodule and one patient (patient 6) was positive with an adrenal