Treatment of Spinocerebellar Ataxia With Mesenchymal Stem Cells:
A Phase I/IIa Clinical Study

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Ataxia is one of the most devastating symptoms of many neurodegenerative disorders. As of today, there is not any effective treatment to retard its progression. Mesenchymal stem cells (MSCs) have shown promise in treating neurodegenerative diseases. We hereby report the results of a phase I/IIa clinical study conducted in Taiwan to primarily evaluate the safety, tolerability, and, secondarily, the possible efficacy of intravenous administration of allogeneic adipose tissue-derived MSCs from healthy donors. Six patients with spinocerebellar ataxia type 3 and one with multiple system atrophy-cerebellar type were included in this open-label study with intravenous administration of 10^6 cells/kg body weight. The subjects were closely monitored for 1 year for safety (vital signs, complete blood counts, serum biochemical profiles, and urinalysis) and possible efficacy (scale for assessment and rating of ataxia and sensory organization testing scores, metabolite ratios on the brain magnetic resonance spectroscopy, and brain glucose metabolism of 18-fluorodeoxyglucose using positron emission tomography). No adverse events related to the injection of MSCs during the 1-year follow-up were observed. The intravenous administration of allogeneic MSCs seemed well tolerated. Upon study completion, all patients wished to continue treatment with the allogeneic MSCs. We conclude that allogeneic MSCs given by intravenous injection seems to be safe and tolerable in patients with spinocerebellar ataxia type 3, thus supporting advancement of the clinical development of allogeneic MSCs for the treatment of spinocerebellar ataxias (SCAs) in a randomized, double-blind, placebo-controlled phase II trials.

Key words: Clinical trials; Allogeneic mesenchymal stem cells (MSCs); Trinucleotide repeat diseases; Gait disorders/ataxia; Spinocerebellar ataxias (SCAs)

INTRODUCTION

Cerebellar ataxia is caused by a functional perturbation of the cerebellum and/or its pathways. Patients with cerebellar ataxia may also manifest additional symptoms, that is, pigmentary retinopathy, extrapyramidal dysfunction, pyramidal signs, cortical symptoms, or peripheral neuropathy. Cerebellar ataxia can be hereditary or sporadic in etiology. Spinocerebellar ataxias (SCAs), the autosomal dominant cerebellar ataxias, consist of more than 30 clinically and genetically heterogeneous neurodegenerative diseases. Multiple system atrophy-cerebellar type (MSA-C) is the most common sporadic form of ataxias in adults.

Spinocerebellar ataxia type 3 (SCA3), also known as Machado–Joseph disease, is the most common autosomal dominant cerebellar ataxia in Taiwan as well as in many countries around the world. The mutation is an unstable CAG triplet repeat expansion in the 3′-coding region of
the ATXN3 gene that encodes ataxin-3 protein containing a polyglutamine tract. In normal alleles, the number of CAG repeats in ATXN3 ranges between 12 and 43, while in mutant alleles the number expands to somewhere between 52 and 86. The expanded CAG repeats result in an excessively long stretch of polyglutamine in the protein product, which would change the protein conformation and, upon degradation by caspasess, would aggregate and cause oxidative stress and eventually premature apoptotic death of neurons. The core clinical feature of SCA3 is a progressive ataxia with unstable gait, vestibular dysfunction, a wide range of visual and oculomotor difficulties, as well as dysarthria and dysphagia.

MSA is a rapidly progressive neurodegenerative disorder manifesting autonomic dysfunction, parkinsonism, cerebellar ataxia, and/or corticospinal tract dysfunction. The neuropathological hallmarks of MSA include neuronal loss, astrogliaisis, and glial cytoplasmic inclusions in the oligodendrocytes. MSA-C represents a predominance of cerebellar symptoms and is noticeably more prevalent among Asians.

As of now, there is still no effective treatment to halt the progression of either SCA3 or MSA, although results of preclinical research of disease modifiers have been encouraging. So far, there have been three double-blind, placebo-controlled, randomized clinical trials using lithium or varenicline in patients with SCA3, as well as riluzole in patients with cerebellar ataxias of different etiologies. Preliminary results suggested some improvements on the Spinocerebellar Ataxia Functional Index (SCAFI) and Composite Cerebellar Functional Score (CCFS) on axial symptoms and rapid alternating movements on the Scale for the Assessment and Rating of Ataxia (SARA) subscores and on International Cooperative Ataxia Rating Scale (ICARS) scores.

Mesenchymal stem cells (MSCs) are multipotent adult stem cells and are capable of differentiating into various cell types, including mesodermal, ectodermal, and endodermal lineages. MSCs also exert their reparative effects through secreting a broad repertoire of trophic factors. MSCs can be used allogeneically given that they express only low major histocompatibility complex class I (MHC-I) and no MHCII, cluster of differentiation 80 (CD80), CD40, or CD86 costimulatory molecules on cell surfaces and therefore lack immunogenicity. Through secreting immune regulatory cytokines, MSCs could also suppress the activation and proliferation of T and B lymphocytes and the differentiation, maturation, and function of dendritic cells. MSCs can be isolated from different sources, including bone marrow (BM-MSCs), umbilical cord blood (UCB-MSCs), dental pulp of the deciduous teeth, and adipose tissues (AD-MSCs). Several preclinical studies in animals showed that MSC infusion could partially restore motor function in SCA mouse models.

Enhanced expressions of neurotrophic factors, such as insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) or glial cell-derived neurotrophic factor (GDNF), were implicated in the neuroprotective mechanisms of MSCs.

In light of all these advances, it seems justified to explore the feasibility of treating patients with cerebellar ataxia with allogeneic MSCs from healthy donors. The purpose of this study was to address the safety, tolerability, and possible efficacy of intravenous (IV) infusion of allogeneic AD-MSCs in patients with cerebellar ataxia.

**MATERIALS AND METHODS**

This pilot, open-label, phase I/IIa clinical trial was approved by the institutional review board (IRB) of Taipei Veterans General Hospital and the Taiwan Food and Drug Administration (TFDA) (ClinicalTrials.gov identifier: NCT01649687). Written informed consent was obtained from all participants before commencement of the study. A data and safety monitoring board (DSMB) composed of four physicians and one statistician was set up to oversee the conduct, integrity, and subject safety.

**Subjects**

Patients with the following characteristics were eligible for the study: (1) aged between 20 and 70 years, (2) meeting the diagnostic criteria of SCA3 or MSA-C, and (3) being scored between 10 and 20 points in the SARA. Patients with one of the following features were excluded: (1) past enrollment, within 30 days, in other cell therapy trial, (2) a positive pregnancy test, or (3) deemed not suitable for the study by the principle investigator. Seven subjects, six with SCA3 and one with MSA-C, met the criteria and were recruited (Table 1).

**Isolation and Culture Expansion of MSCs**

About 100 g of adipose tissues was harvested by liposuction from the abdominal fat of two healthy donors who were negative for hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV) types 1 and 2, human T-lymphotropic virus types 1 and 2, cytomegalovirus, or syphilis, and had a low risk of Creutzfeld–Jakob disease, tuberculosis, as well as other acute or chronic diseases. The mononuclear fraction was harvested after enzymatic digestion and repeated washes and cultivated in T-75 flasks (Thermo Fisher Scientific, MA, USA) in a medium containing 2% fetal bovine serum (FBS; Thermo Fisher Scientific) in a humidified incubator at 37°C under 5% CO₂ for 1 day. Nonadherent cells were then removed by medium replacement. The attached cells, at 70%–80% confluence, were harvested using 0.25% trypsin (Thermo Fisher Scientific) and subcultured. The allogeneic MSCs (Stemchymal; Steminent Biotherapeutics)
Inc., Taipei, Taiwan) were expanded to reach $8 \times 10^8$ cells within 6 weeks.

**Procurement of MSCs**

The MSC products were frozen at a concentration of $7 \times 10^7$ viable cells in 20 ml of cryopreservation solution. All MSCs used in this trial were used at the 12th passage. Trilineage differentiation ability, that is, osteogenic, chondrogenic, and adipogenic differentiation capacity of these cells, was the multipotency test of MSCs before transplantation. Chemistry, manufacturing, and control (CMC) of transplanted cells included controlling the above-mentioned characteristics of MSCs, and all CMC had been approved by the TFDA. The release criteria included (1) a cell viability over 90%; (2) cell surface expressions of CD34−/CD45−/CD11b−/CD19−/human leucocyte antigen (HLA)-DR − ≥ 98% and CD73 +, CD90 +, and CD105 + ≥ 95% as indicated by the flow cytometry; (3) meeting the sterility criteria for bacteria, fungi, and mycoplasma; and (4) the concentration of endotoxin being less than 0.5 EU/ml. On the day of infusion, thawed AD-MSCs were mixed with 100 ml of normal saline and intravenously administered in 40 min.

**Clinical Evaluation**

The study subjects were clinically evaluated 1 month before (baseline) and 0.5, 1, 3, 6, 9, and 12 months after the AD-MSC infusion. Safety monitoring included vital signs, complete blood counts/differential counts, serum biochemical profiles, urinalysis, and occurrence of adverse events (AEs). Efficacy evaluations included clinical assessment with SARA, sensory organization testing (SOT), oculomotor testing, magnetic resonance spectroscopy (MRS), and $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) of the brain.

**SARA**

SARA is a short, user-friendly, semiquantitative clinical rating scale measuring a single factor, ataxia, and consisting of eight components: gait, stance, sitting, speech, finger-chase test, nose–finger test, fast alternating movements, and heel–shin test that yield a total score of 0 (no ataxia) to 40 (most severe ataxia)$^{27}$. SARA has been documented to have high interrater and internal consistencies and satisfies accepted criteria of reliability$^{27}$. The SARA ratings have a good linearity of the scale, and the ceiling effects are negligible. The scores are only weakly associated with disease duration, increase with the disease stage, and are independent of the underlying diagnosis. The natural progression rate of SCA1, 2, 3, 6, and 7 and MSA had previously been documented with SARA among the Chinese in Taiwan$^{28}$.

**Posturography**

SOT is a posturography designed to evaluate an individual’s ability to coordinate the inputs from three sensory systems (visual, vestibular, and proprioceptive) to maintain balance$^{29}$. It was performed with the NeuroCom Smart Balance Master® (NeuroCom International Inc., Clackamas, OR, USA) and quantitatively measured the anterior–posterior body sway given different levels of sensory deprivation and conflicts. The patients, wearing a protective harness that would not limit sway, were asked to stand barefoot on a set area of a platform. Three consecutive trials of six conditions, consisting of different combinations (with eyes opening or closing, platform fixed or movable, and visual background fixed or moving while eyes were opening), were performed while the patients stood still during each 20-s trial. The computer-generated equilibrium scores derived from comparing the patient’s anterior–posterior center of pressure sways with the theoretical maximal limit of stability, which ranges from 0 to 100, with 100 indicating perfect stability, were collected in each trial. A composite equilibrium score from the equilibrium scores of all six conditions with different weightings was then generated to represent the postural steadiness.

**Neuroimaging and Spectroscopic Acquisition**

Magnetic resonance imaging (MRI) and MRS have been shown to be useful in evaluating the morphological and biochemical changes of the cerebellum in patients

<table>
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<th>Patient</th>
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<th>Diagnosis</th>
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<th>Disease Duration (years)</th>
<th>SARA at Baseline</th>
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<td>7</td>
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<td>52/F</td>
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<td>50</td>
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<td>14/73</td>
<td>31</td>
<td>11</td>
<td>13.5</td>
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F: female; M: male; MSA-C: multiple system atrophy-cerebellar type; SARA: Scale for the Assessment and Rating of Ataxia; SCA3, spinocerebellar ataxia type 3.
The parametric ratio images were derived from imaging substations between pre- and posttherapy. The formula of percentage metabolic change (PMC) between two scan images depends on whether we are considering a reduction or an increase in values and is shown below:

$$PMC = \frac{D_{90} - D_{0}}{D_{0}} \times 100\%$$

**Statistical Analysis**

Given the small sample size in this phase I/IIa study, all data were presented as median and first quartile (Q1)–third quartile (Q3) for each variable. The Wilcoxon signed-rank test was used to assess the differences of measurements between before and after treatments. Statistical significance was established at $p<0.05$. The statistical analyses were performed with SAS 9.2 (Cary, NC, USA).

**RESULTS**

All subjects tolerated the procedures well and faithfully and successfully completed the study.

**Safety**

During the 12-month period, 10 AEs were reported, but none of them were graded 3 or 4 in severity or deemed related to the AD-MSC infusion according to the discretion of the DSMB. Subject #2 with MSA-C visited the emergency room (ER) 1.3 months after AD-MSC administration with worsening of preexisting rigidity and depression, requiring a short hospitalization for 5 days [therefore counted as a serious AE (SAE)], with prompt recovery after adjustment of medications. She also had two AEs at 8 months after AD-MSC administration because of similar worsening of preexisting conditions (rigidity, dysphagia, constipation, and depression) but without an ER visit or hospitalization. Subject #6 had a short episode of skin eruptions of brownish scaly papules and plaques on the anterior chest wall at 1.3 months after AD-MSC administration that resolved after topical application of clobetasol ointment. Subject #3 was found to have senile cataract and chronic angle-closure glaucoma at 1.5 months. At 6.5 months, subject #6 was incidentally found to have early diabetes mellitus based on a slightly elevated glycated hemoglobin (6.6%) and a fasting plasma glucose of 107 mg/dl. Two patients with SCA3 had two falls resulting in minor abrasion wounds in the legs (subject #3, at 7th month) and the face (subject #7, at 11th month). Last, subject #3 had one episode of watery diarrhea for 3 days at 10.5 months that recovered spontaneously. No acute or obvious changes in vital signs (Supplementary Table 1, Supplementary Figure 1 available at https://www.dropbox.com/s/jpa32whv2w91biz/20161212%20Supplementary%20material.pdf?dl=0), liver/kidney functions, or levels of C-reactive protein occurred during the
follow-up period in any patient (Supplementary Table 2, Supplementary Figure 2 available at https://www.dropbox.com/s/jpa32whv2w91biz/20161212%20Supplementary%20material.pdf?dl=0). The hematocrit and platelet counts, although slightly reduced compared with the baselines, remained within normal ranges in all patients (Supplementary Table 3, Supplementary Figure 3 available at https://www.dropbox.com/s/jpa32whv2w91biz/20161212%20Supplementary%20material.pdf?dl=0). None of the AEs were deemed, by the DSMB, attributable to the administration of the AD-MSCs.

Clinical Evaluation

**SARA.** The median SARA score in the subjects with SCA3 was 13.25 on entering the trial, which slightly improved to 13 at 0.5 months, 12.75 at 6 months, and returned to 13.5 at 12 months (Fig. 1). The difference in SARA units was −0.25 at 0.5 months, 0 at 6 months, and 0 at 12 months. Although the differences were not statistically significant, given the limited number of subjects, we could discern a trend of improvement that was not seen in our previous natural history study with an observation of a 3-point annual deterioration in SARA scores in ethically similar patients with SCA3. In the single patient with MSA-C (subject #2), no efficacy from MSC treatment was observed.

**SOT.** Two weeks after the AD-MSC infusion, five of six (83%) of patients with SCA3 had a slightly better performance in SOT, compared with their baselines (Fig. 2). After 1, 3, and 6 months, those five patients continued to have a statistically better performance in SOT in the composite score (Fig. 2). The improvement of SOT mainly derived from the patients’ abilities to better integrate sensory inputs from the visual system (p<0.05) to maintain balance (data available upon request). The single patient with MSA-C (subject #2) had her best performance at 6 months (Fig. 2).

**Neuroimaging With MRS.** No significant change in the ratios of metabolites (NAA/Cr or Cho/Cr) was discerned in the cerebellar hemispheres or vermis in any patient during the 12-month follow-up (data available upon request).

**18F-FDG-PET.** The parametric ratio images of PMC between two scan images were adopted to follow the changes of brain glucose metabolism (Fig. 3; quantitative data in Supplementary Table 4 available at https://www.dropbox.com/s/jpa32whv2w91biz/20161212%20Supplementary%20material.pdf?dl=0). At 3 months after treatment, two patients (subjects #2 and #3) demonstrated no apparent changes, two patients (subjects #5 and #6) had a slight improvement, and three patients (subjects #1, #4, and #7) had a reduction in the cerebral and cerebellar glucose metabolism (Fig. 3). At 9 months, a globally improved cerebral and cerebellar glucose consumption was observed in six subjects (Fig. 3). Although the cerebral glucose metabolism of subject #7 improved between 3 and 9 months after treatment, they were still lower than that of the baseline. Subject #5 had a dramatic increment of glucose consumption at 9 months.

**DISCUSSION**

Previously, a randomized, placebo-controlled trial with autologous MSCs in patients with MSA-C demonstrated a clinical efficacy with less deterioration on brain 18F-FDG PET. Another phase I/II trial in patients with SCA reported that IV and intrathecal administrations of human UCB-MSCs did not cause serious transplant-related AEs but rather led to some improvement. Clinical trials with neural stem cell (NSC) engraftment have also demonstrated that cell transplantation is safe. In 2012, allogeneic MSCs were approved to be used as drugs in Canada and New Zealand.

This is the first clinical trial using allogeneic AD-MSCs in patients with cerebellar ataxias. The reason why we used allogeneic, instead of autologous, MSCs was that allogeneic transplantation in a genetic disorder, such as SCA, is conceivably superior. In this case, an autologous transplantation would involve delivering cells with genetic defects. In addition, most of the SCA patients would have difficulty tolerating the abdominal fat aspiration procedure. The allogeneic MSCs from healthy donors would provide a stable and high-quality MSC source in a timely manner. The major concern in this study was the safety and tolerability of the IV administration of allogeneic MSCs. The results indicated that IV infusion of 7×10⁷ allogeneic MSCs was safe and well tolerated. Although several AEs were reported, none of them were attributable to the infusion of allogeneic MSCs. No change in vital signs, hepatic/renal functions, or blood cell counts was observed (Supplementary Tables 1–3, Supplementary Figures 1–3 available at https://www.dropbox.com/s/jpa32whv2w91biz/20161212%20Supplementary%20material.pdf?dl=0).

SARA is a validated and reliable measure of ataxia. Previously, we conducted a longitudinal natural history study in a broadly similar group of patients and learned that patients with SCA3 would likely deteriorate 3.00±1.52 SARA points annually. Relative to the natural progression, patients with SCA3, with injection of MSCs, appeared to have an initial, albeit brief, burst of improvement in the first 2 weeks to 1 month (Fig. 1), followed by stabilization of the natural progression of the disease at
the end of the 1-year follow-up period. Data in the SOT seemed to corroborate this observation (Fig. 2). Although this phase I study did not allow us to have the statistical luxury of having a real placebo control group, the previous natural history control study showed us that the trend would have been worse in the absence of the intervention. This “difference-in-differences” suggests that AD-MSC treatment might have been more efficacious in retarding the progression of SCA3 if higher doses of AD-MSCs were administered. These pieces of evidence of “lessened progression” are very encouraging.

Several mechanisms of MSC therapeutics have been proposed, including neuroprotection by secreting neurotrophic factors, immunomodulation, angiogenesis, etc.

Figure 1. The longitudinal changes in Scale for the Assessment and Rating of Ataxia (SARA) scores. (A) At the 6-month follow-up, compared with the baseline, SARA scores seemed improved in two (subjects #6 and #7), remained unchanged in two (subjects #3 and #4), and worsened in two (subjects #1 and #5) of the six patients with spinocerebellar ataxia type 3 (SCA3). In the single patient with multiple system atrophy-cerebellar type (MSA-C) (subject #2), a slight worsening of SARA score was observed. At 1-year follow-up, SARA scores remained better in one (subject #6), unchanged in three (subjects #3, #5, and #7), and worsened in two (subjects #1 and #4) patients with SCA3. A marked worsening of SARA score was observed in the patient with MSA-C (subject #2). (B) Adipose tissue-derived mesenchymal stem cell (AD-MSC) infusion seemed to stabilize/retard the disease progression compared with the natural history of the ethnically similar patients with SCA-3, in whom SARA score worsened by an average of 3 points per year.
and mitigation of reactive oxygen species (ROS)\textsuperscript{39}. Although transplanted cells may not transdifferentiate into cerebellar Purkinje cells, the predominant therapeutic mechanism of engrafted human MSCs may likely be secretion of neurotrophic factors, which may have improved the rotarod performance of SCA2 mice\textsuperscript{23}. Intravenously infused human MSCs did extravasate and migrate into the cerebellar white matter and cerebral cortex, and the MSCs administered through the IV route or local injection both preserved the numbers of Purkinje cells in the SCA mice\textsuperscript{23}. Recently, Mendonca et al.\textsuperscript{40} found that cerebellar NSCs transplanted into the cerebellum of adult SCA3 transgenic mice were able to differentiate into neurons, astrocytes, and oligodendrocytes and salvage the pathological changes with reduction of Purkinje cell loss, cerebellar layer shrinkage, and mutant ATXN3 aggregates. Some of the cerebellar NSCs remained undifferentiated and likely contributed to neuroprotection by reducing neuroinflammation, increasing the levels of neurotrophic factors, and triggering an alleviation of the motor behavior impairments. Likewise, it is plausible that IV-infused allogeneic MSCs might exert

**Figure 2.** The longitudinal changes in sensory organization testing (SOT). (A) Patients with SCA3 (n=6) seemed to have better composite scores during the 0.5- to 6-month follow-ups (p<0.05 at 3 and 6 months). The patient with MSA-C (subject #2) seemed to have a peak response at 6 months (30 points improved). (B) Overall, intravenous (IV) administration of allogeneic adipose tissue-derived mesenchymal stem cells (AD-MSCs) seemed to stabilize the progression of SCA3.
their effects through secreting paracrine or immune-modulatory factors. It might also be remotely possible that they might migrate into the cerebellum, integrate into the circuits, and replenish the degenerated cells. Further preclinical studies using labeled AD-MSCs to track the migration, distribution, engraftment, and transdifferentiation of AD-MSCs in the CNS after IV infusion will answer these key questions. The therapeutic mechanism of IV-transplanted MSCs in treating SCA patients needs to be elucidated in the phase II trial.

The intriguing results of the PET studies suggested that a single, low-dose IV infusion of AD-MSCs might have a lasting effect in rescuing the compromised cerebral/cerebellar glucose metabolism. The apparent discordance between the timing of the metabolic improvement and the minimal clinical improvement suggests that the changes in brain metabolism were probably not biologically meaningful at the low dose of MSCs. A future longitudinal study in a larger cohort given a higher dosage of MSCs would be desirable to demystify the discordance.
In an earlier and separate study that took place over a period of 2 years, we found that MRS was not a sensitive marker to longitudinally track the changes of brain atrophy in patients with cerebellar ataxias\textsuperscript{41}. Therefore, the lack of MRS changes in this trial after only 1 year was not surprising.

The limitation of this phase I/IIa study is the lack of placebo controls and limited number of patients enrolled. Given the small sample size, the results could only suggest the tolerability and safety of the treatment.

In conclusion, the safety and tolerability of a single IV administration of allogeneic MSCs at a dosage of 7×10\textsuperscript{7} cells was demonstrated in this phase I/IIa clinical trial. A trend toward brief improvement and lasting stabilization of the disease was discerned in the limited number of patients. A larger-sized, randomized, double-blinded, placebo-controlled phase II clinical trial appears justified to further confirm the safety profile and therapeutic potential of the allogeneic MSC treatment for ataxia. A dose- and frequency-finding design would be desirable in the next phase. There is also a pressing need to develop better biomarkers (i.e., proteins or miRNAs in the serum or cerebrospinal fluid) to correlate with and reflect the severity of ataxia.

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