Case report

Multiple transplantation of mesenchymal stem cells in a patient with active progressive multiple sclerosis: Long term therapeutic outcomes

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Multiple sclerosis (MS) is one of the most common idiopathic inflammatory demyelinating disease. One of the challenges in the treatment of MS is how to overcome relapses without severe adverse effects. Due to their immunoregulatory properties and safety, mesenchymal stem cells (MSCs), present a potential alternative for treatment for MS. The efficacy and safety of a long-term MSCs therapy in MS remain to be established. In this communication, we report the clinical condition and disease progression of an MS patient treated for 11 years, with multiple infusions of MSCs derived from either his bone marrow (BM), pooled human umbilical cords (UC), or from his own child umbilical cord. A male patient diagnosed as progressive MS (EDSS score 3) was enrolled into our study and received 1 × 10^6 cells/kg of MSCs, at least once a year for 9 years. The MSCs treatment was well tolerated with no significant side effects. Following the transplantation of MSCs, the overall EDSS scores of the patient decreased over the 10 years period of observation. MRI investigation did not reveal any new lesions. However, upon the cessation of the MSCs treatment, the EDSS score increased from 1.0 to 3.5, further supporting the notion that in such a patient, the transplantation of MSCs, had a significant beneficial effect. This case study is the first to report on the beneficial effects of multiple infusions of BM-MSC and umbilical cord mesenchymal stem cells (UC-MSCs) in a progressive MS patient, over a period of 11 years, in absence of any other treatments. Hence, multiple infusions of MSCs may provide a novel therapeutic avenue for patients with aggressive MS.

1. Introduction

Multiple sclerosis (MS) is one of the most common idiopathic inflammatory demyelinating disease. One of the challenges in the treatment of MS is how to overcome relapses without severe adverse effects. Due to their immunoregulatory properties and safety, mesenchymal stem cells (MSCs), present a potential alternative for treatment for MS. The efficacy and safety of a long-term MSCs therapy in MS remain to be established. In this communication, we report the clinical condition and disease progression of an MS patient treated for 11 years, with multiple infusions of MSCs derived from either his bone marrow (BM), pooled human umbilical cords (UC), or from his own child umbilical cord. The MSCs treatment was well tolerated with no significant side effects. Following the transplantation of MSCs, the overall EDSS scores of the patient decreased over the 10 years period of observation. MRI investigation did not reveal any new lesions. However, upon the cessation of the MSCs treatment, the EDSS score increased from 1.0 to 3.5, further supporting the notion that in such a patient, the transplantation of MSCs, had a significant beneficial effect. This case study is the first to report on the beneficial effects of multiple infusions of BM-MSC and umbilical cord mesenchymal stem cells (UC-MSCs) in a progressive MS patient, over a period of 11 years, in absence of any other treatments. Hence, multiple infusions of MSCs may provide a novel therapeutic avenue for patients with aggressive MS.
was enrolled in our clinical study, which approved by the ethics committee, and a written informed consent was obtained from the patient for being treated with multiple transfusions of MSCs. This clinical study aimed to exploring the effects and safety of mesenchymal stem cells transplantation for severe and refractory multiple sclerosis (MS). Initially the patient was infused with his bone marrow-derived stem cells, according to our previously published procedure [1]. From 2008 to January 2010, he received 3 intravenously as well as 3 intrathecal infusion of BM-MSCs.

As the patient stabilized, UC-MSCs were subsequently used for the transplantation. From August 2009 to December 2018, he received a total of 12 intravenous infusions of UC-MSCs, in absence of any other disease-modifying therapy (DMT). The isolation, culture methods and quality control of UC-MSCs used for this patient have been previously described [2,3].

From 2010–2016, UC-MSCs were obtained from voluntary donors attending the Yan an Hospital affiliated of Kunming Medical University, in January 2016, the UC-MSCs source used for this patient changed as he became father, and thus the MSCs were harvested from the umbilical cord of his healthy baby. when his wife gave birth. Details of UC-MSCs infusion route, dosage and timepoints are shown in the Table 1. The patient remained well after the UC-MSCs therapy, showing only transient fatigue and drowsiness, immediately after the administration of MSCs. As indicated in Fig. 2, his EDSS score decreased to 1.5 in 2013 and was maintained at that level until 2017. By 2018, his EDSS score was further reduced to 1.0, a drop of some 2.5 points, from the time he was first enrolled in our study. While we cannot exclude the possibility that the EDSS score improvement seen in this patient is due to a natural recovery, these data demonstrated that the multiple infusions of MSCs are probably quite safe and are possibly associated with anti-inflammatory effects. In this context, it is interesting to note that upon the cessation of the UC-MSCs during the second half of 2017, this patient relapse. By 2019, his EDSS score went from 1.0 (in 2018) to 3.5, the level at which he was enrolled in our study. These changes are in line with the MRI data which showed that in 2017, the T2-weighted positive abnormalities were decreased in number and size in the white matter as well as spinal cord (Fig. 1). Moreover, it was noted that the edema around the lesions were reduced and some of the lesions had turned to an inactive status. However, by 2019, a number of new lesions appeared.

### Table 1

| Date       | MSC source | Route | Dose    | EDSS score |
|------------|------------|-------|---------|------------|
| Pre-treatment |            |       |         |            |
| 06/09/2006  | UC-MSCs    | iv    | 1.32 × 10^5 | 3.0        |
| 26/11/2008  | BM-MSCs    | iv    | 6.3 × 10^6  | 3.5        |
| 19/02/2009  | BM-MSCs    | it    | 6.0 × 10^7  | 2.5        |
| 07/05/2009  | BM-MSCs    | iv    | 1.4 × 10^7  | 2.5        |
| 04/08/2009  | BM-MSCs    | iv    | 8.9 × 10^7  | 2.0        |
| 08/01/2010  | BM-MSCs    | iv    | 1.2 × 10^8  | 2.0        |
| 29/08/2010  | UC-MSCs    | iv    | 3.27 × 10^8 | 2.0        |
| 22/04/2011  | UC-MSCs    | iv    | 1.4 × 10^9  | 2.0        |
| 29/12/2011  | UC-MSCs    | iv    | 1.51 × 10^9 | 2.0        |
| 04/09/2012  | UC-MSCs    | iv    | 8.65 × 10^9 | 2.0        |
| 22/09/2013  | UC-MSCs    | iv    | 1.07 × 10^9 | 1.5        |
| 15/01/2015  | UC-MSCs    | iv    | 1.66 × 10^9 | 1.5        |
| 06/01/2016  | UC-MSCs    | iv    | 9.1 × 10^9  | 1.5        |
| 21/04/2016  | UC-MSCs    | iv    | 5.09 × 10^9 | 1.5        |
| 22/07/2016  | UC-MSCs    | iv    | 9.32 × 10^9 | 1.5        |
| 28/03/2017  | UC-MSCs    | iv    | 1.03 × 10^10| 1.5        |
| 22/09/2017  | UC-MSCs    | iv    | 7.0 × 10^10 | 1.5        |
| Post-       |            |       |         |            |
| treatment  2018 |         |       | 1.0     |            |
| Post-       |            |       |         |            |
| treatment  2019 |         |       | 3.5     |            |

MSCs: mesenchymal stem cells.
BM-MSCs: bone marrow mesenchymal stem cells.
UC-MSCs: umbilical cord mesenchymal stem cells.
EDSS: Expanded Disability Status Scale.
iv: intravenous injection.
it: intrathecal injection.

### Discussion

It is now well established that disease modifying therapies (DMTs) are quite effective in controlling acute inflammation but far less efficient in repairing tissues and delaying disease progression [4]. The limited therapeutic options for severe forms of MS made stem cells therapy a potential new therapeutic option. Here, we report on a patient with progressive MS, according to the temporal and spatial multiple evidences from MRI results, EDSS scores and Cerebrospinal Fluid (CSF) examination. In previous clinical trials of mesenchymal stem cells, the follow-up period was from 12 to 26 months. The majority of these trials indicated early signs of clinical improvement in most patients by 3 months and maintained up in different time periods [5–7]. Our study extends these findings by studying the long term effect of multiple MSCs infusions in MS patients to a period of some 11 years. As recently reviewed [6], the majority of severe side effects such as transient encephalopathy and headache that are observed following MSCs therapy relate to their intrathecal administration. By contrast, the most common adverse reactions in our study were fatigue and drowsiness, a finding in line with those reported by Connick et al. [6].

It is noteworthy that following the BM/UC-MSCs treatment, our patient with a progressive MS, showed a significant improvement in his EDSS score over time and this in the absence of any disease modifying therapy (eg glucocorticoid pulse). The treatment which consisted of 16 MSCs infusions, administrated over more than a decade period, was overall well tolerated and lead to an apparent clinical and radiological disease recovery. Indeed, the MRI examinations performed from 2008 until 2018, confirmed the absence of subclinical disease activity, a finding in agreement with other MSCs transplantation studies in MS [8–11]. However, as highlighted here, the cessation of UC-MSCs infusion has the great potential of leading to disease recurrence. This is taken to indicate that the potential immunoregulatory effect of MSCs may not be long lasting.

The major purpose of our study is to evaluate the safety of the UC-MSCs treatment in the long term. Although the combined MSCs treatment may compromise the immune system and increase the risk of organ disorders and tumor generation, none of the side effects were observed during the 11-years follow-up, suggesting the MSCs treatment is potentially safe. Because the source of the cells (umbilical or bone marrow) different and the number of cells varied in each treatment in the current study, it is insufficient to make any conclusions on treatment efficiency. More patients should enrolled to get detailed data and provided more supporting evidences.

In summary, this is to the best of our knowledge, the first long term study that report on the efficacy and safety of multiple BM/UC-MSCs infusions given as a therapeutic approach to a progressive MS in absence of any other medications. The study showed that such BM/UC-
MSCs therapy appeared safe, is well tolerated and leads to an improvement in the quality of life in our patient. Of particular note is the continuous improvement we witnessed over the 10 years of treatment both clinically and pathologically. Intermittent as well as regular treatment with BM/UC-MSCs transplantation alone may represent a novel therapeutic strategy for aggressive case of MS, larger randomized, placebo controlled and double blinded clinical trials should be undertaken to further assess the safety and efficacy of MSCs in MS.

Ethics approval and consent to participate

The approval was obtained from the Ethics Committee of Yan’an Hospital affiliated to Kunming Medical University. The procedures of the study were performed according to the Declaration of Helsinki and the patients gave written informed consent before enrollment.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

References

[1] Z.L. Hou, Y. Liu, X.H. Mao, C.Y. Wei, M.Y. Meng, Y.H. Liu, Z. Zhuyun Yang, H. Zhu, M. Short, C. Bernard, Z.C. Xiao, Transplantation of umbilical cord and bone marrow-derived mesenchymal stem cells in a patient with relapsing-remitting multiple sclerosis, Cell Adhes. Migr. 7 (5) (2013) 404–407.

[2] Mingyao Meng, Wenju Wang, Chuanyu Wei, Feife Liu, Zhiqin Du, Yanhua Xie, Weiwei Tang, Zongliu Hou, Qihan Li, Umbilical cord mesenchymal stem cell transplantation in the treatment of multiple sclerosis, Am. J. Transl. Res. (2018).

[3] F.F. Konen, P. Schwenkenbecher, K.F. Jendretzky, S. Gingele, L. Grote-Levi, N. Möhn, K.W. Sühls, B. Eiz-Vesper, B. Maecker-Kolhoff, C. Trebst, T. Skripuletz, M. W. Hümmert, Stem cell therapy in neuroimmunological diseases and its potential neuroimmunological complications, Cells 11 (14) (2022) 2165.

[4] M.M. Bonab, M.A. Sahraian, A. Aghaie, S.A. Karvigh, S.M. Hosseinian, B. Nikbin, J. Lotfi, S. Khorrarnia, M.R. Motamed, M. Toghi, M.H. Harirchian, N. B. Moghadam, K. Alkhani, S. Yadegari, S. Jafari, M.R. Ghenei, Autologous mesenchymal stem cell therapy in progressive multiple sclerosis: an open label study, Curr. Stem Cell Res. Ther. 7 (6) (2012) 407–414.

[5] B. Yamout, R. Hourani, H. Salti, W. Barada, T. El-Hajj, A. Al-Kutoubi, A. Herlopian, E.K. Baz, R. Mahfouz, R. Khalil-Hamdan, N.M. Kridieh, M. El-Sabban, A. Bazarchi, Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: a pilot study, J. Neuroimmmunol. 227 (1–2) (2010) 185–189.

[6] P. Connick, M. Kolappan, C. Crawley, D.J. Webber, R. Patani, A.W. Michell, M. Q. Du, S.L. Lan, D.R. Altmann, A.J. Thompson, A. Compston, M.A. Scott, D. H. Miller, S. Chandran, Autologous mesenchymal stem cells for the treatment of...
secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study, Lancet Neurol. 11 (2) (2012) 150–156.

[7] O. Fernandez, G. Izquierdo, V. Fernandez, L. Leyva, V. Reyes, M. Guerrero, A. Leon, C. Arnaiz, G. Navarro, M.D. Paramo, A. Cuesta, B. Soria, A. Hmadcha, D. Pozo, R. Fernandez-Montesinos, M. Leal, I. Ochotorena, P. Galvez, M.A. Geniz, F. J. Baron, R. Mata, C. Medina, C. Caparros-Escudero, A. Cardesa, N. Cuende, Research Group Study Eudra CT, Adipose-derived mesenchymal stem cells (AdMSC) for the treatment of secondary-progressive multiple sclerosis: a triple blinded, placebo controlled, randomized phase I/II safety and feasibility study, PLoS One 13 (5) (2018), e0195891.

[8] B. Yamout, R. Hourani, H. Salti, W. Barada, T. El-Hajji, A. Al-Kutoubi, A. Herlopian, E.K. Baz, R. Mahfouz, R. Khalil-Hamdan, N.M. Kreidieh, M. El-Saban, A. Bazarbachi, Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: a pilot study, J. Neuroimmunol. 227 (1–2) (2016) 185–189.

[9] J.P. Holloman, C.C. Ho, A. Hukki, J.L. Huntley, G.I. Gallicano, The development of hematopoietic and mesenchymal stem cell transplantation as an effective treatment for multiple sclerosis, Am. J. Stem Cells 2 (2) (2013) 95–107.

[10] O. Fernandez, G. Izquierdo, V. Fernandez, L. Leyva, V. Reyes, M. Guerrero, A. Leon, C. Arnaiz, G. Navarro, M.D. Paramo, A. Cuesta, B. Soria, A. Hmadcha, D. Pozo, R. Fernandez-Montesinos, M. Leal, I. Ochotorena, P. Galvez, M.A. Geniz, F. J. Baron, R. Mata, C. Medina, C. Caparros-Escudero, A. Cardesa, N. Cuende, Research Group Study Eudra CT, Adipose-derived mesenchymal stem cells (AdMSC) for the treatment of secondary-progressive multiple sclerosis: a triple blinded, placebo controlled, randomized phase I/II safety and feasibility study, PLoS One 13 (5) (2018), e0195891.

[11] Z. Lu, L. Zhu, Z. Liu, J. Wu, Y. Xu, C.J. Zhang, IV/IT hUC-MSCs Infusion in RRMS and NMO: a 10-Year Follow-Up Study, Front. Neurol. 11 (2020) 967.