INFORMATION BRIEF (RAPID REVIEW)

MESENCHYMAL STEM CELL FOR CHILDREN WITH AUTISM

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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Rapid Review
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TITLE: MESENCHYMAL STEM CELL FOR CHILDREN WITH AUTISM

PURPOSE

To review the effectiveness, safety and cost-effectiveness of mesenchymal stem cell for children with autism based on request from the Director General of Health who received a proposal from a clinician for compassionate use of the stem cells in autism children.

BACKGROUND

Autism spectrum disorders (ASDs) are one of the most prevalent neurodevelopmental disorders among children today. About 1 in 44 children has been identified with ASD in 2018 according to estimates from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network.[1] There are currently no epidemiological data on the prevalence of autism in Malaysia.[2] However, based on a feasibility study on the use of Modified Checklist for Autism in Toddlers (MCHAT) among children of 18 to 36 months of age in childhealth clinics by Ministry of Health Malaysia in 2006, the prevalence of ASD in Malaysia was reported to be approximately 1.6 in 1000. [3]

The treatment of ASD is variable and multimodal. It is composed of conventional therapies, such as social skills training, early intensive behaviour therapy, applied behaviour analysis, speech therapy, occupational therapy, together with psychotropic drugs. Among the new therapies available, are gene therapy and stem cell therapy.[4]

Around the world, scientists are researching stem cells source with great potential for regenerative medicine. The current review highlights recent findings in the areas of hMSCs (human MSCs) sources, its ex vivo differentiation ability, immunogenicity, homing ability, banking and cryopreservation, its role in the treatment of chronic diseases and its use in human clinical trials. [5] Mesenchymal stem cells are classically defined as formative pluripotential blast cells found inter alia in bone marrow, blood, dermis and periosteum that are capable of differentiating into any of the specific types of mesenchymal or connective tissues. These cells are routinely generated by culture of bone marrow in various culture media and collection of the adherent cell population. An important characteristic of mesenchymal stem cells is their ability to constitutively secrete immune inhibitory factors such as interleukin 10 (IL-10) and transforming growth factor-β (TGF-b) while maintaining ability to present antigens to T cells. The ability of mesenchymal stem cells on one hand to suppress pathological immune responses but on the other hand to stimulate haematopoiesis leads to the possibility that these cells may also be useful for treatment of the defect in T cell numbers associated with autism.[6]

EVIDENCE SUMMARY

There were 73 articles retrieved on the mesenchymal stem cell for children with autism from the scientific databases such as Medline, EBM reviews, Pubmed and from the general search engines [Google Scholar and US Food and Drug Administration (USFDA)] using the search term *autism, autistic disorder, kanners syndrome, autism spectrum disorder, stem cell therapy, mesenchymal stem cell, adipose tissue derived mesenchymal stem cell, bone marrow stromal cell.* Last search was conducted on 26th April 2022. Only four studies were included in this review, consisted of one systematic review with meta-analysis, one randomised controlled trial, one case series and one case report

EFFICACY/ EFFECTIVENESS

Villarreal-Martinez L et al. conducted a systematic review with meta-analysis to assess safety and efficacy of stem cell treatments and analyse their effects on the cognitive and behavioural impairments in patients diagnosed with autism. They systematically searched for the controlled and non-controlled, randomised and non-randomised trial evaluating stem cell therapy as a treatment for autism in patients with autism spectrum disorder compared to placebo or without comparator. Study selection, data collection and risk of bias assessment were conducted by four independent reviewers and any discrepancies were discussed. Primary outcome of interest was improvement in clinical scales. A total of 11 studies with 461 patients were included in the review. The trials sample sizes ranged from 12 to 18 patients, from two to 33 years of age and had follow up ranging from six to 26 months. Six studies administered infusion of autologous umbilical cord blood cells, three studies administered bone marrow stem cell transplantation, one study administered intravenous infusion of mesenchymal stromal cells and one study administered foetal stem cell transplantation. Fourteen scales were reported; however, meta-analysis was conducted on the Autism Behaviour Checklist (ABC) scale, Childhood Autism Rating Scale (CARS) scale and Vineland Adaptive Behaviour Scales (VABS) scale which is reported in two or more articles. The result was reported in mean raw or unadjusted mean (MARW).[7]

The meta-analysis reported that, the mean raw value for ABC scale was -11.97 (95 % CI -91.45 to 67.52) and CARS scale was -9.08 (95 % CI -15.43 to -2.73). Meanwhile, VABS scale was reported by their domains such as communication domain mean raw 2.69 (95 % CI 1.30 to 4.08), daily living domain mean raw 1.99 (95 % CI 0.83 to 3.15); motor domain mean raw 1.06 (95 % CI -0.37 to 2.48), socialisation domain mean raw 3.09 (95 % CI 1.71 to 4.48) and adaptive behaviour domain mean raw 2.10 (95 % CI 1.04 to 3.16). The most common side effects reported included fever, hyperactivity, vomiting, headache, and aggressiveness.[7]

An RCT was conducted by Sharifzadeh N et al. to determine the safety and efficacy of treatment with autologous bone marrow mesenchymal stem cells (BMMSCs) compared with

routine treatment in children with ASD. A total of 32 children aged five to 15 years were randomly assigned to either autologous BMMSC plus rehabilitation therapy and risperidone (intervention group) or rehabilitation therapy and risperidone (control group). Autologous BMMSCs were intrathecally injected in the intervention group twice in four weeks. Patients were assessed using CARS, Gilliam autism rating scale- second edition (GARS-II) and clinical global impression (GCI) at baseline, as well as at six and 12 months after intervention. They reported that, there was no significant improvement in CARS total score, GARS-II index and CGI between the groups over 12 months. The main effect for time and group interaction was significant regarding the CGI-severity of illness, showing a significantly more pronounced improvement in the intervention group ($F=6.719$; $p=0.002$).[8]

Kobinia GS et al. reported a case series on four children that were diagnosed with autism at ages between two to four years. They received autologous bone marrow derived, intrathecal and simultaneous intravenous point of care stem cell transplant (SCT) at ages of four to 14 years old. The outcome was reported by parents using the Autism Treatment evaluation checklist (ATEC) score comprises of speech communication, sociability, sensory or cognitive awareness and heath physical or behaviour. A higher score indicate a higher impairment. They found that, there was reduction in the ATEC total score from between 31 to 50 point pre- SCT (moderate) to below than 30 point (mild) post- SCT in the patients. Post assessment ranged from nine months to one year. They also reported no minor or major complication due to procedure.[9]

Maric DM et al. also reported a case of an autism patient aged four years who received intrathecal autologous bone marrow nuclear cells transplantation along with neurorehabilitation. The children were assessed using GARS-II consist of stereotypical behaviour, social interaction and communication subscale. They reported that there was reduction in GARS-II score from 142 (autism index of 99%) to 91 (autism index of 27%).[10]

SAFETY

There was no evidence retrieved on safety of the mesenchymal stem cell therapy among the children with autism. The only stem cell-based products that are FDA-approved for use in the United States consist of blood-forming stem cells (haematopoietic progenitor cells) derived from cord blood. Those products are approved for limited use in patients with disorders that affect the body system that is involved in the production of blood. However, there was no evidence retrieved from the USFDA website regarding the approval of stem cell therapy to treat autism.[11]

COST-EFFECTIVENESS

There was no evidence retrieved on the cost-effectiveness of mesenchymal stem cell therapy among the children with autism. The estimated cost for the mesenchymal stem cell therapy is approximately ranged from USD1,000 to USD 100,000 depending on the patients' condition.[12]

CONCLUSION

There was very limited evidence retrieved to suggest that mesenchymal stem cell therapy may improve the clinical outcome such as communication, daily living, social and adaptive behaviour among the autistic children. Hence, more study is needed to support the use of mesenychymal stem cell for children with autism.

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