INPLASY PROTOCOL

To cite: Chen et al. Effectiveness of gene therapy for motor function in children with spinal muscular atrophy: a systematic review and meta-analysis of randomized controlled trials. Inplasy protocol 202350072. doi: 10.37766/inplasy2023.5.0072

Received: 18 May 2023

Published: 18 May 2023

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Support: **No any financial support.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

Effectiveness of gene therapy for motor function in children with spinal muscular atrophy: a systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: **To identify the efficacy of gene therapy for motor function in children with spinal muscular atrophy (SMA); to compare effects and safety of potential different treatments for SMA.**
Condition being studied: **Spinal muscular atrophy (SMA) is a neurodegenerative disorder caused by mutations in SMN1 (encoding survival motor neuron protein (SMN)). Reduced expression of SMN leads to loss of α-motor neurons, severe muscle weakness and often early death. Estimated incidence is 1 in 6,000 to 1 in 10,000 live births and carrier frequency of 1/40-1/60. This disease is characterized by generalized muscle weakness and atrophy predominating in proximal limb muscles, and phenotype is classified into four grades of severity (SMA I, SMAII, SMAIII, SMA IV) based on age of onset and motor function achieved.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 May 2023 and was last updated on 18 May 2023 (registration number INPLASY202350072).

INTRODUCTION

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METHODS

Search strategy: A comprehensive literature search was undertaken using the following electronic bibliographic databases, involving PubMed, Web of Science, Ovid MEDLINE, Scopus, EMBASE, Cochrane Library, CINAHL plus databases, until to May 2023. search terms include spinal muscular atrophy, gene therapy, diseases modifying treatment, gene replacement therapy, gene implantation therapy, AVXS-101, spinraza, nusinersen, evrysdi, risdiplam, zolgensma, onasemnogene abeparvovec, motor function, upper limb function, motor milestone, RULM, MFM, CHOP INTEND, HINE-2, 6MWT, revised upper limb module, 6-minute walk test, motor function measure, Hammersmith functional motor scale-expanded, Hammersmith infant neurological examination-II, children's hospital of Philadelphia infant test of neuromuscular disorders.

Participant or population: Children with SMA aged <18 years (i.e. SMA type 1, 2 and 3) will be included in the study. SMA type 1 is the mostsevere and common type, which accounts for about 50%of patients diagnosed with SMA. Classically infants withSMA type I have onset of clinical signs before 6 monthsof age, never acquire the ability to sit unsupported and,if no intervention is provided, generally do not survivebeyond the first 2 years. SMA type 2 is characterized by onset between 7 and18 months of age. Patients achieve the ability to situnsupported and some of them are able to acquirestanding position, but they do not acquire the ability towalk independently. SMA type 3 includesclinically heterogeneous patients. They typically reach allmajor motor milestones, as well as independent walking.

Intervention: gene therapy, diseases modifying treatment, gene replacement therapy, gene implantation therapyGene therapy approaches have been evaluated for SMA, using viral vec.

Comparator: Standard care, supportive therapy, routine/conventional therapy, combination treatment or placebo/ controlAny interventions or combinations in addition to gene therapy.

Study designs to be included: RCT.

Eligibility criteria: PICO principles were followed, identifying: population (children with 5q SMA < 18 years in any settings); intervention (gene therapy or disease-modifying treatment or gene replacement therapy); comparison (standard care, supportive therapy, routine/conventional therapy, combination treatment or placebo/ control); and outcome (valid and reliable measurements identified for motor function or upper limb function in SMA). Study designs were limited to RCTs published in English language, with a clear statement of appropriate ethics approval. Studies were excluded if they were patients who complicated additional neurological conditions other than SMA; not gene therapies. Conference abstracts, animal studies, grey literature, unpublished studies were also excluded. Full articles that were not available also excluded.

Information sources: A comprehensive literature search was undertaken using the following electronic bibliographic databases, involving PubMed, Web of Science, Ovid MEDLINE, Scopus, EMBASE, Cochrane Library, CINAHL plus databases, until to May 2023. Conference abstracts, animal studies, grey literature, unpublished studies were also excluded. Full articles that were not available also excluded.

Main outcome(s): The valid and reliable measurements identified for motor function or upper limb function in SMA, including HFMSE, HINE-2, CHOP INTEND, MFM, 6MWT.

Quality assessment / Risk of bias analysis: The methodological quality was independently assessed by two authors (CB and ZTT) using the Cochrane Risk of Bias 2 (ROB2) assessment tool. The tool includes five different domains: (1) bias arising from the randomization process; (2) bias due to deviation from intended interventions; (3) bias due to missing data; (4) bias in measurement of the outcome; and (5) bias in the selection of the reported results, with an overall risk of bias also advocated. Any disagreements were discussed with the corresponding author (GYL).

Strategy of data synthesis: We conducted meta-analyses after synthesizing all the available data by using Cochrane Collaboration software. (Review Manager Version 5.1). Weighted mean differences with 95% confidence intervals (CIs) were used to analyze continuous outcomes, while dichotomous outcomes were summarized using odds ratio (OR) and 95% CIs. The presence of heterogeneity among studies was assessed using the I2 and Chi2 tests. In cases where significant statistical heterogeneity was observed (I2 ≥ 50%, P < 0.10), a random-effects model was utilized; whereas, a fixed-effect model was employed when there was no heterogeneity detected (I2 < 50%, P > 0.10).

Subgroup analysis: The potential different commercial gene therapies or different type of SMA could be undertaken a subgroup analysis if appropriate.

Sensitivity analysis: Where sensitivity analyses identify particular decisions or missing information that greatly influence the findings of the review, try and resolve uncertainties and obtain extra information by contacting authors and obtained individual patient data.

Language restriction: Study designs were limited to RCTs published in English language.

Country(ies) involved: China.

Keywords: Spinal muscular atrophy, gene therapy, motor function.

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