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## Spinal muscular atrophy: An update of therapeutic approaches.

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Spinal muscular atrophy (SMA) is an autosomal recessive disorder that affects motor neurons (MNs). It is caused by mutations in the survival motor neuron gene 1 (SMN1) **(1)**. The SMN2 gene, which is the highly homologous SMN1 copy that is present in all patients, is unable to prevent the disease. The clinical characteristics of SMA vary widely. The disorder can appear soon after birth, or not until adulthood. Patients are clinically classified into three main subtypes. Type I, the severe form, affects infants before the age of six months and these children never sit unaided (usually type 0 SMA, the most severe congenital form, is included in this group). Type II is the intermediate form and it has an onset after six months; these children never walk unaided. Type III is the mild form and it affects patients after 18 months. Patients in this group are able to walk but they may later lose this ability (usually type IV SMA, the mildest form of the disease starting in the second or third decade of life is included in this group). This classification is useful to help doctors communicate with each other internationally to developing strategies for clinical trials **(2)**. Treatment for SMA is a major challenge because the clinical variations between patients are extensive. To design suitable clinical trials we therefore need to take many factors into account. These include the type of SMA, the patient's age, the severity status of the disease, the type of therapeutic approach, the timing of the proposed intervention in relation to disease progression, the availability of a reliable marker for prognostic and evolution of the disease and the relative homogeneity of the group under study. The disease manifests itself according to the amount of protein that an individual may produce. This is directly related to the number of SMN2 copies that a patient may have. Most SMA patients have 2 to 3 copies from a possible range of 1 to 5 copies **(3)**. The lack of both SMN1 and SMN2 genes has never been described indicating that the SMN protein is crucial for life although it is unknown why MNs are so sensitive to SMN depletion. The explanation for the neuromuscular phenotype in SMA is to assume that insufficient SMN protein causes motor neuron dysfunction and death, and that muscle atrophy is a consequence of denervation. However, investigation is ongoing to ascertain whether muscle, neuromuscular junctions, or motor neurons alone are the critical target tissue in

SMA. The study of terminal peripheral nerves and neuromuscular junctions identify possible links between the two tissues in the pathogenesis of the disease. Indeed, the involvement of neuromuscular junctions in SMA was recently demonstrated during human development **(4)** confirming previous reports from mice models **(5)**.

Two main therapeutic strategies emerge as suitable in SMA. The first strategy directly addresses the genetic defect via SMN2 stimulation or via SMN1 replacement. The second strategy is an SMN-independent approach that aims to protect motor neurons and skeletal muscle. Specific approaches may include: 1) To increase the amount of complete SMN protein produced by the SMN2 gene by small molecules or antisense oligonucleotides; 2) To protect motor neurons (MNs) from damage by neuroprotective agents or by cell therapy; 3) To increase muscle strength and endurance by different compounds and 4) To deliver normal copies of SMN 1 in MNs by gene transfer (gene therapy) **(6)**. It seems likely that therapy would be more effective if combinations of these approaches will be used and if earlier SMA detection will be implemented by neonatal screening. In the meantime that these new strategies are proven to be effective, proactive measures regarding nutrition, physical therapy and respiratory care may alleviate clinical symptoms and improve quality of life of patients **(7)**.

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