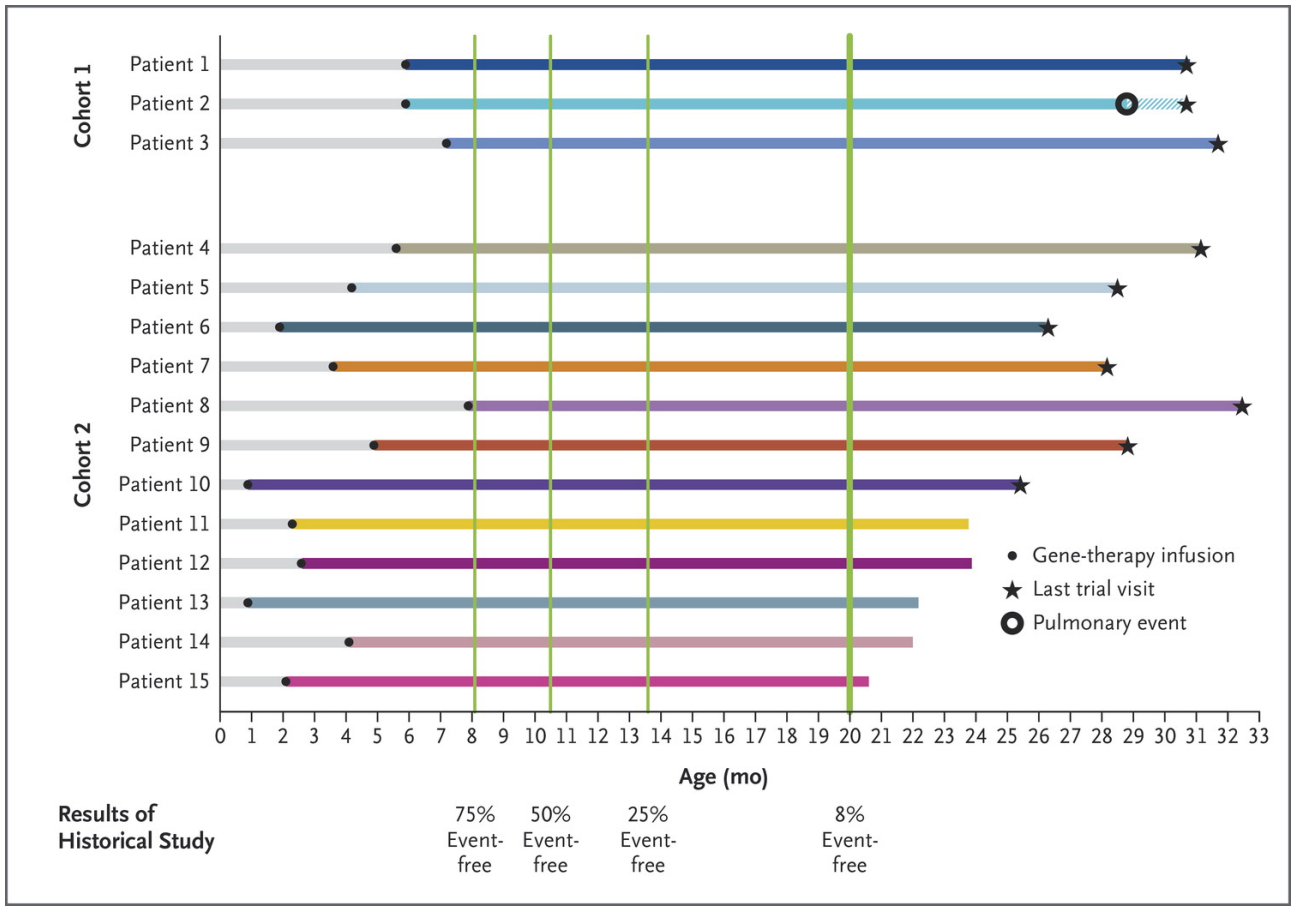
TERAPIE INNOVATIVE PER LA SMA – NEJM 2 NOV 2017-11-20

Entro 20 mesi la maggior parte dei bimbi affetti da Atrofia Muscolare Spinale sarebbe già in cielo.

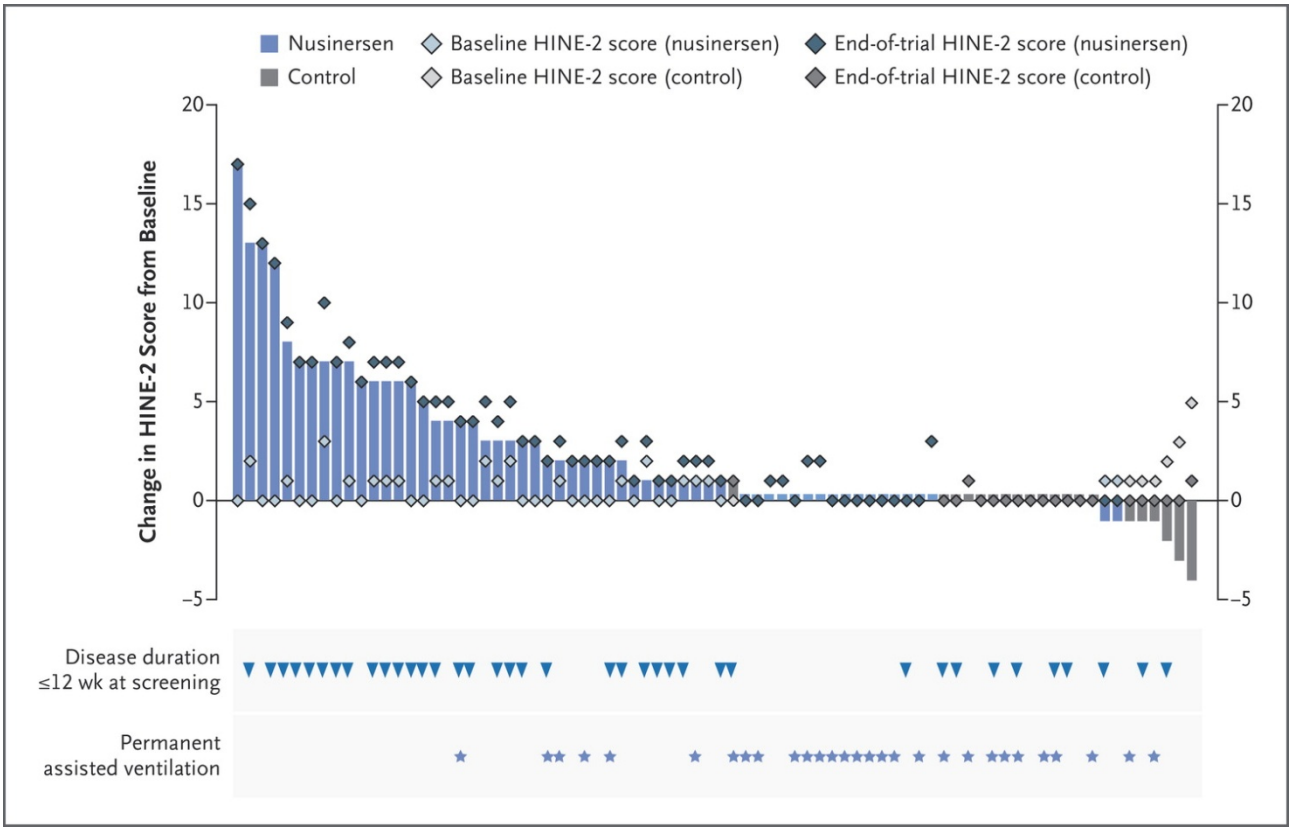
La Atrofia Muscolare Spinale è dovuta da una delezione omologa nel gene SMN1 , che produce una ridotta espressione della proteina essenziale al neurone motore (SMN) con la progressiva degenerazione dei moto neuroni.

Una dose singola di un Adenovirus 9 che porta il DNA complementare che codifica per la proteina SMN mancante sembra fare la differenza.



In alternativa alla terapia genica viene impiegato il NUSINERSEN , un oligonucleotide anti senso che modifica lo splicing dell' RNA pre-messaggero del gene difettoso SMN2, e così promuove l'incremento della produzione di una proteina SMN a lunghezza normale.

Il grafico fa vedere che la grande maggioranza dei bambini trattati migliora notevolmente lo sviluppo neuro motorio.



Vi allego l'Editoriale che accompagna i due articoli.

The Dilemma of Two Innovative Therapies for Spinal Muscular Atrophy

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If you have made a diagnosis of spinal muscular atrophy (SMA) type 1 (also known as Werdnig–Hoffman disease) in a child, then you have vivid memories of informing desperate parents that there is nothing you can do for their child. Two innovative therapies for SMA may now bring some hope — but what do they mean for patients and their families?

SMA, which is one of the most common inheritable neuromuscular diseases, is a degenerative motor neuron disorder that leads to muscle atrophy and respiratory failure. Patients with the most severe form rarely survive beyond 2 years of age. The disease is caused by defects in the gene encoding survival motor neuron (SMN) 1 (*SMN1*), but a paralogous gene, *SMN2,* also produces SMN protein. *SMN2* is subject to aberrant pre–messenger RNA splicing, with variable skipping of exon 7, that leads to production of normal SMN protein at only 5 to 10% of the normal level. A person may carry several copies of *SMN2*; the presence of more copies of *SMN2* leads to increased production of normal SMN protein. This largely explains the spectrum of disease severity; affected patients range from weak infants to ambulant children and adults. The most severe and prevalent form of the disease is SMA type 1, which accounts for 60% of cases of SMA. Two studies presented in this issue of the *Journal* focus on SMA type 1.

The therapeutic approaches in these two studies have a common objective: to increase the production of SMN protein in motor neurons and thereby improve motor function and survival. Mendell et al.1 investigated the use of gene therapy, which involved a single intravenous administration of nonreplicating adenovirus (scAAV9 [self-complementary adeno-associated viral serotype 9]) vector that included the normal human *SMN1* sequence. Finkel et al.2 investigated the use of an antisense approach that was designed to prevent the exclusion of exon 7 in *SMN2,* which involved repetitive intrathecal administration of the antisense oligonucleotide drug nusinersen. This multicenter, randomized, sham-

controlled trial was preceded by several smaller, phase 1–2 studies involving infants with SMA type 1 and children 2 to 14 years of age with SMA type 2 or 3 that had generally positive results.[3,4] The scAAV9 gene therapy has not yet been approved,[1] whereas nusinersen was approved for use in children and adults with SMA by the Food and Drug Administration in 2016 and by the European Medicines Agency this year.[2,5,6]

Both Mendell et al. and Finkel et al. found significant improvement in motor outcomes and survival. In the trial of nusinersen, which enrolled 122 infants with onset of symptoms at 6 months of age or younger, a significantly larger proportion of infants in the nusinersen group than infants in the control group achieved motor milestones (41% vs. 0%). At a prespecified interim analysis, the trial was terminated. In the final analysis, the proportion of infants in the nusinersen group who achieved motor milestones increased to 51%. However, there is room for improvement. Of the infants who achieved motor milestones, only 8% could sit independently and 1% could stand. By the end-of-trial cutoff date, 39% of the infants in the nusinersen group and 68% in the control group had died or received permanent assisted ventilation. The best results were observed in patients who started treatment within 13 weeks after the onset of disease.

The study of scAAV9 gene therapy was an open-label, phase 1–2 study that enrolled 15 patients.[1,7,8] Three patients received a low dose of gene therapy (6.7×10^{13} vg per kilogram of body weight), and 12 received a high dose (2×10^{14} vg per kilogram). No patients in the low-dose group achieved any of the normal motor milestones, and 1 became dependent on ventilatory support. The high-dose group had better results: 9 patients were able to sit without support for at least 30 seconds, and 2 were able to crawl, pull to stand, and walk independently. At the last assessment, all the patients in both cohorts were alive and at least 20 months of age; in the high-dose group, 7 of the 10 patients who did not require ventilatory support at baseline still did not require such support. Because of the different study designs, it is hard to compare the results of these two studies; in addition, the mean age of the patients was slightly lower in the study of scAAV9 gene therapy than in the trial of nusinersen (3.4 months vs. 5.4 months).

An important advantage of scAAV9 gene therapy is that it may require only a single intravenous infusion, whereas nusinersen probably requires lifelong repetitive intrathecal treatment. Follow-up has been short in both studies, and the durability of the effects is uncertain for both treatments. If the expression of the scAAV9 gene therapy declines over time, the same treatment may not be able to be repeated, because antibodies against AAV capsid proteins are anticipated to form. As the children grow, the phenotype may expand to affect other organs and tissues, which would then require confirmation that therapies such as scAAV9 and antisense oligonucleotides target other cell types.[3,7-10]

Neither therapy currently provides a cure. One option may be to start treatment earlier; the NURTURE study (ClinicalTrials.gov number, NCT02386553) is currently investigating the effect of nusinersen in presymptomatic patients. Another option is to combine the two treatments. An important constraint is the high anticipated cost of $750,000 for a course of nusinersen during the first year of therapy.

Treating children with SMA brings new responsibilities and unique dilemmas. Doctors will need to take greater care than ever before in following patients through standardized assessments and guiding families in decision making.