Therapeutic decision-making under uncertainty in the management of Spinal Muscular Atrophy: results from DECISIONS-SMA study

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Supplementary Material

1. **Hypothetical case scenarios as presented to participants (answers in bold were considered suboptimal treatment decisions)**

1. A 5-month-old patient recently diagnosed of SMA type 1 still does not sit up. You observe mild suction and swallowing difficulties. CHOP INTEND=28.

   i) On a scale from 1% to 100%, what are your expectations of improvement in 2 years for this patient with any of the treatments currently available?

   ii) Which of the following options would you choose? CHOOSE 1 OPTION ONLY

   - Intrathecal drug with loading dose and subsequent administration every 4 months.

   - Oral drug with daily administration.

   - Intravenous drug with single administration.

   - **Start combined treatment with sodium valproate and L-carnitine.**

   - **Do not initiate drug treatment, start rehabilitation program and reassess the patient in 6 months.**

2. SMA type 1 patient on treatment with nusinersen since 6 months of age with controlled motor milestones. The patient is currently 18 months old and has started to walk (CHOP INTEND=54; HMFSE=48), but has swallowing difficulties and is starting to have a wet voice.

   Which of the following options would you choose? CHOOSE 1 OPTION ONLY

   - **Continue current treatment.**

   - Discontinue current treatment and start oral drug with daily administration.

- **Continue current treatment and reinforce with speech therapist (including respiratory rehabilitation) to improve patient's bulbar functions.**

- Discontinue current treatment and start a drug with a different mechanism of action that acts on the SMN1 gene.

- **Continue current treatment and reinforce with speech therapist (including respiratory rehabilitation) with virtual reality to improve patient's bulbar functions.**

3) SMA type 1 patient treated with nusinersen since 6 months of age who at 2 years of treatment has not achieved the expected motor milestones.

Which of the following options would you choose? CHOOSE 1 OPTION ONLY

- **Continue current treatment.**

- Discontinue current treatment and start oral drug with daily administration.

- Discontinue current treatment and start gene therapy.

- **Continue current treatment and reinforce with rehabilitation therapy with virtual reality to improve motor function.**

- **Discontinue current treatment and reinforce with rehabilitation therapy with virtual reality to improve motor function.**

4) A 3-year-old SMA type 1 patient who has received treatment with onasemnogene abeparvovec at the onset of symptoms. In the last 2 months has begun to have difficulty to run and climb stairs. The patient's HINE score has decreased 4 points versus the baseline assessment.

Which of the following options would you choose? CHOOSE 1 OPTION ONLY

- Start oral treatment with daily administration.

- **Intensify motor rehabilitation program as the main treatment line.**

- Start intrathecal treatment with administration every 4 months.

- **Do not initiate new treatment, start rehabilitation program and reassess patient in 6 months.**

- **Start combined treatment with sodium valproate and L-carnitine.**

5) A 4-year-old SMA type 2 patient who has remained stable without treatment, but currently with decreased independence for activities of daily living and increased fatigue.

Which of the following options would you choose? CHOOSE 1 OPTION ONLY

- Intrathecal drug with loading dose and subsequent administration every 4 months.

- Oral drug with daily administration.

- Intravenous drug with single administration.

- **Intensify motor rehabilitation treatment to maintain/improve patient's daily functions (without drug).**

- **Start emotional support and motor rehabilitation to maintain/improve patient's daily functions (without drug).**

6) A 1-year-old patient recently diagnosed with SMA type 2. You discuss treatment options with the parents. Parents have no preferences in treatment administration options.

   i) On a scale from 1% to 100%, what are your expectations of improvement in 2 years for this patient with any of the treatments currently available?

   ii) Which of the following options would you choose? CHOOSE 1 OPTION ONLY

- Intrathecal drug with loading dose and subsequent administration every 4 months.

- Oral drug with daily administration.

- Intravenous drug with single administration.

- **Intensify motor, respiratory and swallowing rehabilitation treatment to maintain/improve patient's daily functions (without drug).**

- Combine gene therapy with oral drug.

- Combine gene therapy with intrathecal drug.

7) A 6-year-old SMA type 2 patient treated with nusinersen with a decrease in motor milestones at 2 years of treatment and a 3-point reduction in the HMFSE (currently 58) versus baseline.

Which of the following options would you choose? CHOOSE 1 OPTION ONLY

- **Continue current treatment.**

- Discontinue current treatment and start oral drug.

- **Continue current treatment and rehabilitation and closely monitor the patient.**

- Discontinue current treatment and start gene therapy.

- **Discontinue current treatment and check on patient's progress in 3 months.**

8) A 5-year-old SMA type 2 patient treated with nusinersen for 2 years with slight worsening of motor function and a 1-point reduction in the HMFSE (baseline 50, current 49).

Which of the following options would you choose? CHOOSE 1 OPTION ONLY

- Continue current treatment and monitoring.

- **Discontinue current treatment and start oral treatment.**

- Continue current treatment and rehabilitation and closely monitor the patient.

- **Discontinue current treatment and start gene therapy.**

- **Discontinue current treatment and check on patient's progress in 3 months.**

9) A 2-year-old SMA type 2 stable patient treated with nusinersen for 2 years who had a 6-point improvement in the HMFSE (current 58). The parents report that the child is beginning to have difficulties eating by himself.

Which of the following options would you choose? CHOOSE 1 OPTION ONLY

- **Continue current treatment.**

- Discontinue current treatment and start oral drug.

- **Continue current treatment and rehabilitation and closely monitor the patient.**

- Discontinue current treatment and start gene therapy.

- **Discontinue current treatment and check on patient's progress at three months.**

10) A 16-year-old SMA type 2 patient with a history of late diagnosis, currently in a wheelchair and limited mobility in upper limbs. No current treatment for SMA.

i) On a scale from 1% to 100%, what are your expectations of improvement in 2 years for this patient with any of the treatments currently available?

ii) Which of the following options would you choose? CHOOSE 1 OPTION ONLY

- Intrathecal drug with loading dose and subsequent administration every 4 months.

- Oral drug with daily administration.

- Intravenous drug with single administration.

- **Do not initiate new treatment, start rehabilitation program and reassess patient in 6 months.**

11) A 15-year-old SMA type 2 ambulant patient diagnosed at 3 years of age. No treatment received and currently stable regarding motor milestones over the last 2 years.

   i)   On a scale from 1% to 100%, what are your expectations of improvement in 2 years for this patient with any of the treatments currently available?

   ii)   What drug would you choose as first treatment option if all were available?

- Intrathecal drug with loading dose and subsequent administration every 4 months.

- Oral drug with daily administration.

- Intravenous drug with single administration.

- **Do not initiate new treatment, start rehabilitation program and reassess patient in 6 months.**

2. Concepts from behavioral economics

From the behavioral economics perspective, uncertainty includes two different concepts: risk and ambiguity. Risk is defined as the preference for a safe option when the probability of an outcome is known (e.g.: oral anticoagulation for stroke prevention among patients with atrial fibrillation offer a 65-75% risk reduction for a recurrent event compared to 20-25% of antiplatelet agents).

Ambiguity is a concept that involved decisions when the probability of an event is unknown. Ambiguity aversion is a cognitive bias defined as dislike for events with unknown probability

over events with known probability. For example, an ambiguity-averse individual would rather choose a treatment where the probability of benefits or side effects are known over one where these probabilities are unknown. In the present study, we focused on ambiguity aversion as defined by the experiment illustrated in the figure. Specifically, participants were asked to choose between a visual option with known 50/50 probability of winning 400 or 0 Euros versus an option with unknown probability of the same outcomes. Grey bars represented the degree to which probability was unknown. This information was sequentially presented in pairs (50/50 option with one of the scenarios representing increasing probability of ambiguity). The degree of ambiguity aversion was defined as the number of scenarios that participants chose the 50/50 option over the ambiguous option (reflects as a score of n/5; where n represents the number of times participants choose the 50/50 option and 5 the total number of presented scenarios).
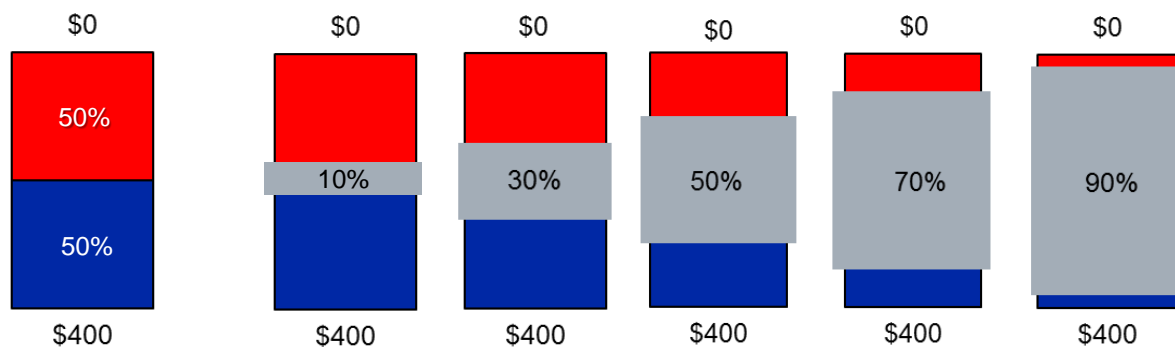
3. **Models testing the association between occupational burnout and treatment initiation, escalation and therapeutic inertia**

Outcome: Lack of treatment initiation for naïve patients with SMA

```
      Source |       SS           df       MS      Number of obs   =        35
-------------+----------------------------------   F(4, 30)        =      1.87
       Model |  15.8004923         4  3.95012308   Prob > F        =    0.1415
    Residual |  63.3423648        30  2.11141216   R-squared       =    0.1996
-------------+----------------------------------   Adj R-squared   =    0.0929
       Total |  79.1428571        34  2.32773109   Root MSE        =    1.4531
```

```
--------------------------------------------------------------------------------
   Tx initiation | Coefficient  Std. err.      t    P>|t|    [95% conf. interval]
-----------------+--------------------------------------------------------------
            age  |   .2087708   .1186905     1.76   0.089    -.0336276    .4511692
  yrs_experience |  -.2338444   .1265703    -1.85   0.075    -.4923354    .0246466
   nm_specialist |   .4766864   .5931553     0.80   0.428    -.7346982    1.688071
    work burnout |    1.23611   .5937088     2.08   0.046     .0235948    2.448625
           _cons |  -3.077711   3.470666    -0.89   0.382    -10.16576    4.010335
--------------------------------------------------------------------------------
```

Outcome: Lack of treatment escalation (switches)

```
      Source |       SS           df       MS      Number of obs   =        35
-------------+----------------------------------   F(4, 30)        =      2.43
       Model |  10.5706545         4   2.64266362  Prob > F        =    0.0690
    Residual |  32.5722027        30   1.08574009  R-squared       =    0.2450
-------------+----------------------------------   Adj R-squared   =    0.1444
       Total |  43.1428571        34   1.26890756  Root MSE        =     1.042

--------------------------------------------------------------------------------
  tx_switches   | Coefficient  Std. err.      t    P>|t|    [95% conf. interval]
----------------+---------------------------------------------------------------
            age |   .1594691   .0851123     1.87   0.071    -.0143535    .3332917
 yrs_experience |  -.1911581   .0907629    -2.11   0.044    -.3765206   -.0057957
  nm_specialist |    .760517   .4253484     1.79   0.084    -.1081603    1.629194
   work burnout |    1.01344   .4257453     2.38   0.024     .1439524    1.882928
          _cons |  -1.182732   2.488796    -0.48   0.638    -6.265531    3.900066
--------------------------------------------------------------------------------
```


Outcome: Therapeutic inertia for all simulated case scenarios

```
      Source |       SS           df       MS      Number of obs   =        35
-------------+----------------------------------   F(4, 30)        =      2.00
       Model |  17.5967963         4   4.39919908  Prob > F        =    0.1200
    Residual |  66.0032037        30   2.20010679  R-squared       =    0.2105
-------------+----------------------------------   Adj R-squared   =    0.1052
       Total |        83.6        34   2.45882353  Root MSE        =    1.4833

--------------------------------------------------------------------------------
      TI_score  | Coefficient  Std. err.      t    P>|t|    [95% conf. interval]
----------------+---------------------------------------------------------------
            age |   .2175698   .1211578     1.80   0.083    -.0298674    .4650071
 yrs_experience |  -.2491303   .1292014    -1.93   0.063    -.5129947    .0147342
  nm_specialist |   .6949896   .6054855     1.15   0.260    -.5415768    1.931556
   work burnout |   1.327988   .6060505     2.19   0.036     .0902676    2.565708
          _cons |  -2.461044   3.542813    -0.69   0.493    -9.696433    4.774345
--------------------------------------------------------------------------------
```