Pharmacology of neurodegenerative diseases

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Definition of neurodegeneration

- Irreversible death of neurons resulting in progressive impairment of neuronal function
- Pathogenesis:
  - Overfunction of the excitatory amino acids → apoptosis
  - Oxidative stress
- Etiology
  - Autoimmune process
  - Prion
  - Viral infection
  - Metabolic disorder
  - Genetic inheritance
  - Trauma
  - Arteriosclerosis
  - Inflammatory diseases

Most important diseases

- Parkinson's disease
- Alzheimer's disease
- Huntington's chorea
- Vascular dementia
- Wilson's disease
- Multiple sclerosis (autoimmune)
- Amyotrophic lateralsclerosis (ALS)
- Spinal muscular atrophy (SMA)

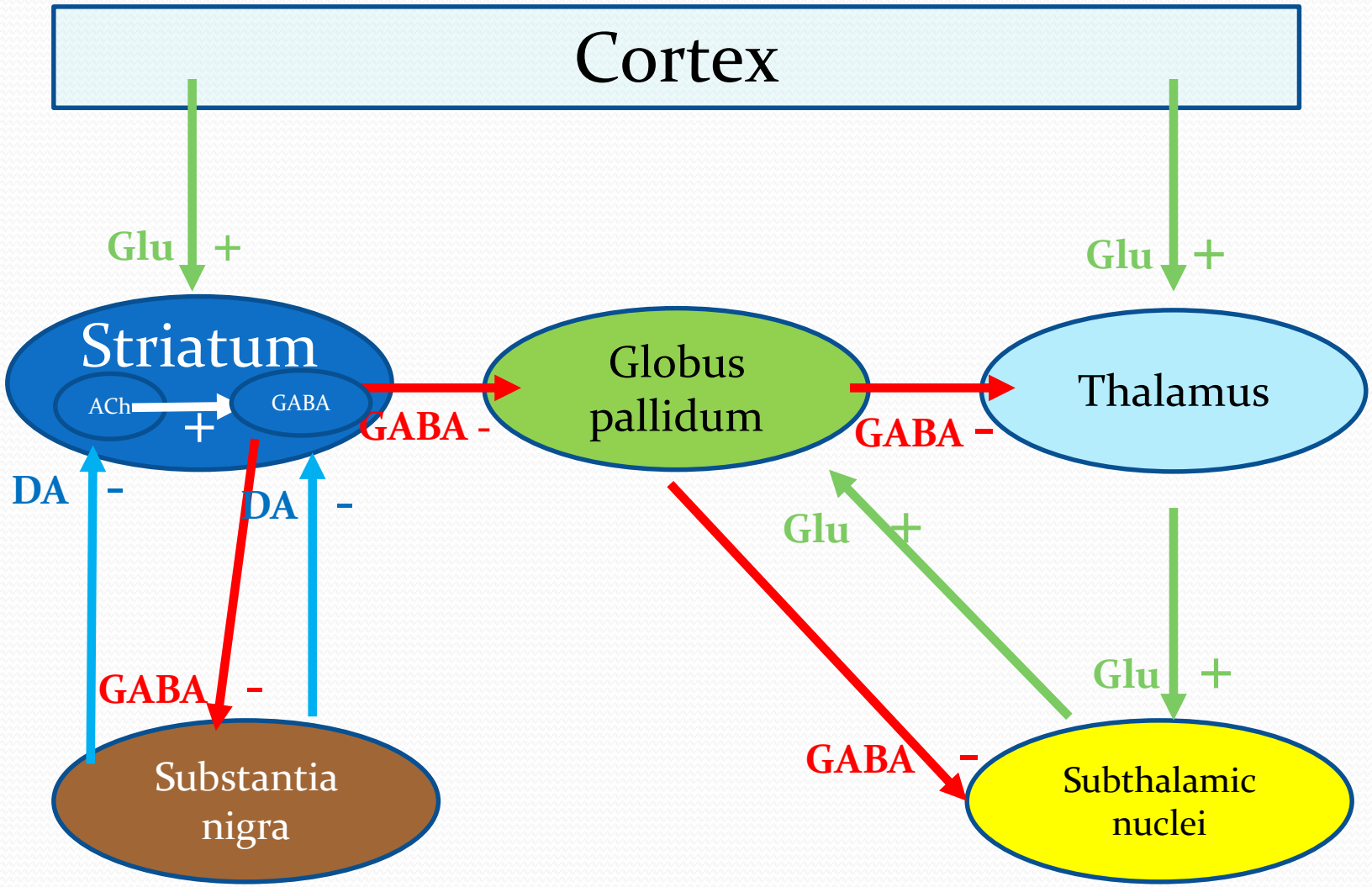
Parkinson's disease (PD)

James Parkinson published in 1817 six cases about patients having simptoms of paralyisis agitans

Symptoms:
-**A**kinesia/hypokinesia
-Muscle **r**igidity
-Resting **t**remor
-Unstable **p**osture

ART classification:
-Akinetic-rigid form – bad prognosis
-Tremor-dominant form – slow progression

Extrapyramidal motoric control



Pathophysiology of Parkinson's Disease

- Multisystem disease
  - Main lesion: Degeneration of cells in the substantia nigra pars compacta (SNpc) that produce dopamine, a neurotransmitter responsible for the regulation of excitatory and inhibitory outflow of the basal ganglia
  - Many other brain structures are affected, explaining the wide spectrum of motor and non-motor manifestation of PD
  - Prevalence: ~ 1 % of the population above 65 years
  - 10% of the Parkinson's disease starts around 40 years
- The etiology of PD is unknown
  - Environmental factors
  - Genetic factors
- Only known risk factor is age

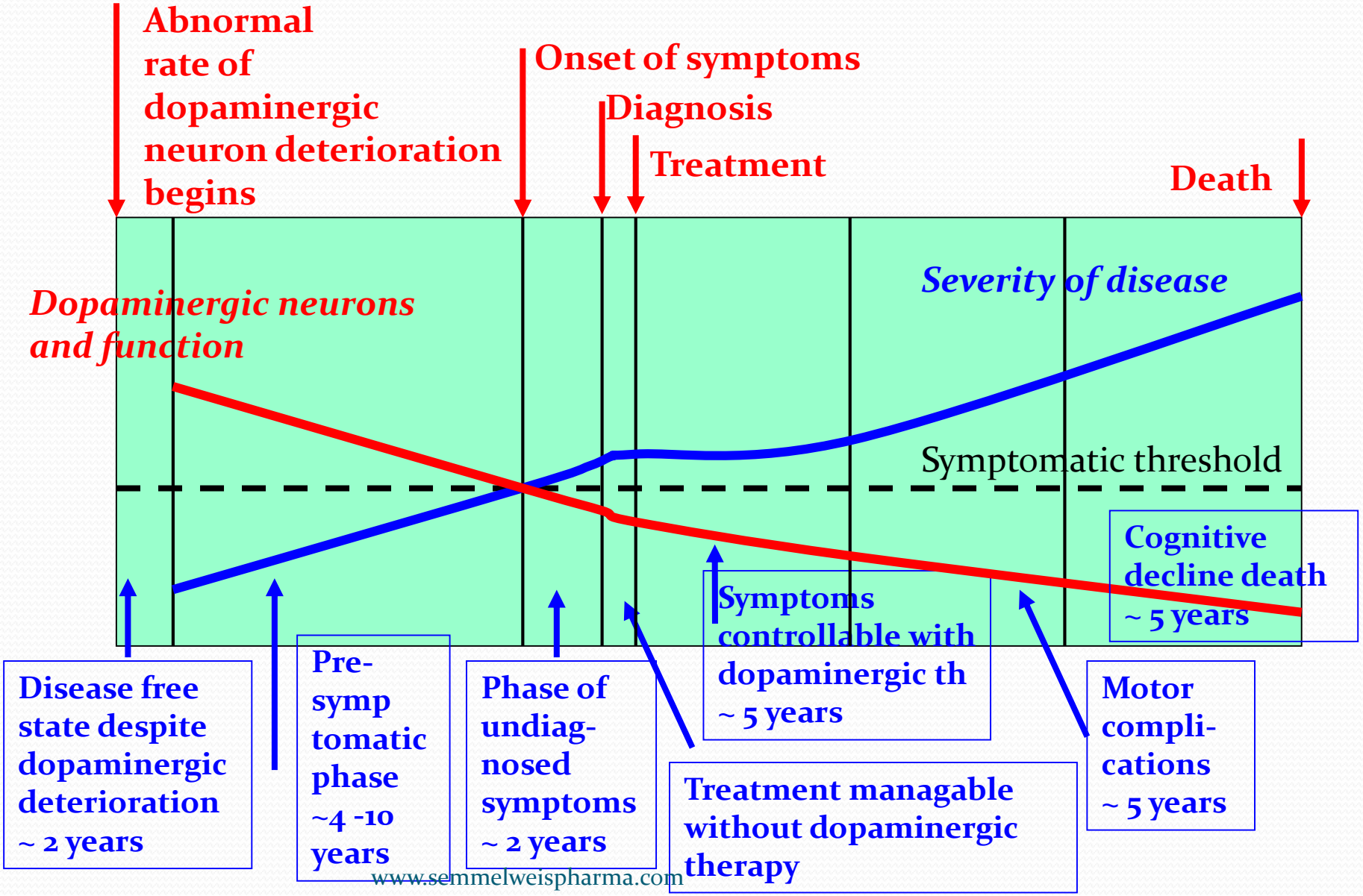
Etiology of Parkinson's disease

1. Neurotoxicity by free oxygen radicals – SOD dysfunction may lead to oxidative stress. Dopamine is metabolized by MAO-B – free oxygen radicals are forming → dopamine can be considered as a "dopaminergic neuronkiller"

   This may explain the typical age of appearance (around 60)
2. Viral infection – supported by the disease called encephalitis letargica after the Spanish flu pandemia
3. Toxic theory – supported by the selective toxicity of MPTP originally a contamination in a street-drug

Phases and course of PD

Jankovic J Parkinson's Disease and related neurodegenerative disorders. Pharmacia & Upjohn 1997



Clinical criteria for diagnosis of PD

- Motoric manifestations:
  - Resting tremor
  - Bradykinesia
  - Rigidity
  - Postural instability, which occurs later in the course of the disease
- Diagnostic criteria:
  - Bradykinesia
  - At least 1 of:
    - Muscular rigidity
    - 4-6 Hz resting tremor
    - Postural instability

Clinical criteria for diagnosis of PD

- **Supportive symptoms for diagnosis (≥ 3):**
  - Unilateral onset
  - Resting tremor
  - Progressive signs and symptoms
  - Persistent asymmetry of signs
  - Excellent early response to levodopa; response for ≥ 5 years
  - Levodopa-induced dyskinesias
  - Clinical course > 10 years

Clinical spectrum of PD

MOTORIC SYMPTOMS (see earlier)

NON-MOTOR SYMPTOMS

- **Cognitive/psychiatric dysfunction:**
  - Cognitive impairment and dementia (verbal fluency, visuospatial processing, and executive function)
  - Psychosis
  - Depression
  - Anxiety

Clinical spectrum of PD

- **Sleep dysfunction:**
  - Insomnia
  - Parasomnias (rapid eye movements, behavior disorder, nightmares, hallucinations)
  - Excessive daytime sleepiness
  - Sudden onset of sleep
  - Other sleep-related disorders (restless leg syndrome, obstructive sleep apnea)
- **Sensory symptoms:**
  - Pain
  - Paresthesias
  - Olfactory dysfunction

Clinical spectrum of PD

- **Autonomic dysfunction:**
  - Orthostatic hypotension
  - Impaired gastrointestinal motility
  - Constipation
  - Swallowing difficulties
  - Heat intolerance
  - Urinary symptoms (frequency, urgency)
  - Impotence
  - Hyperhidrosis
  - Hypersalivation
  - Seborrhea

Therapy of Parkinson's disease

- Dopamine side
  - Substitution (levodopa)
  - MAO-B inhibitors
  - Dopamine agonists
  - COMT inhibitors
- Glutamate pathway???
  - Amantadine
- Acetylcholine side
  - Centrally acting anticholinergic drugs

Substitution therapy – levodopa

Levodopa

- Lack of dopamine → providing the precursor levodopa (dopamine canot be given, does not cross BBB)
- Pharmacokinetics:
  - Good oral absorption
  - Time to reach peak concentration (t_{max}): 1-2 hours
  - Plasma half-life: 1-3 hours
- Only 1-3% enters the brain due to extensive peripheral metabolism by DOPA-decarboxilase

Substitution therapy – levodopa (continuation)

- Enhancement of penetration:
  - Combination with peripherally acting DOPA-decarboxilase inhibitors – carbidopa, benserazide
  - MONOTHERAPY IS NEVER APPLIED
  - COMT inhibitors (entacapone, opicapone) can be added, they reduce levodopa-induced dyskinesias

- Penetration can be increased up to 12% → levodopa dose can be reduced down to one quarter of the monotherapy dose

Substitution therapy – levodopa (continuation)

- Adverse effects
  - Acute peripheral: nausea, vomiting (tolerance develops against them), arrhythmias, orthostatic hypotension
  - Acute central: depression, psychosis (paranoid reactions), agitation, anxiety, nightmares
  - Chronic: acceleration of progression (recently questioned)
    - End of dose phenomenon – shorter duration of action – narrowing dosing intervals
    - On-off phenomenon – levodopa induced dyskinesia (choreoathetoid dyskinesia) in on phase – akinesia in off phase. Normal movement cannot be achieved.

Substitution therapy – levodopa (continuation)

Therapeutic consideration:

to start as late as possible

MAO-B inhibitors

- Selegiline [(-)-deprenyl]
- Rasagiline
- Safinamide

- Inhibition of dopamine metabolism
- Selegiline is neuroprotective (enhancement of scavanger function – superoxide dismutase and catalase activity)

- Other indications of selegiline: Alzheimer's disease, depression

Dopamine D_2-agonists

- Ergot derivatives:
  - bromocryptine, cabergoline
- Non-ergot derivatives:
  - pramipexole(oral), ropinirole (oral), rotigotine (patch)
    apomorphine (injection)
- Adverse effects:
  - Similar to levodopa: nausea, vomiting, constipation, dyspepsia, postural hypotension, arrhythmias, dyskinesias, confusion, hallucinations, delusions, impulse control disorders (gambling, shopping, hypersexual activity, etc.)

COMT-inhibitors

- Prolong the action of levodopa
- Entacapone and opicapone
  - Inhibits the peripheral metabolism of levodopa by COMT enzyme
  - Decrease substitution therapy induced motoric fluctuations
- Tolcapone
  - Similar effect but it has a central component as well
  - Hepatotoxic

Amantadine

- Originally an antiviral drug (influenza prevention)
- Uncertain mechanisms:
  - NMDA-antagonist
  - Enhancing dopamine by inhibiting its reuptake or stimulating its release and synthesis
  - Adenozine A_{2A}-receptor antagonist → disinhibition of D_2-mediated effects
- Weaker than levodopa and tolerance develops against it
- Therapeutic usefulness in akinetic crisis
- Mainly mental side-effects

Centrally acting anticholinergic drugs

- Acetylcholine M-receptor antagonists
- Good CNS penetration
- Procyclidine, biperiden, trihexyphenidyl, orphenadrine, dexethimide, metixene, benztropine
- Mainly for drug-induced Parkinsonism
- Effect is good on tremor and rigidity, minimal efficiency against hypokinesia
- Atropine-like side-effects

Pros and Cons of available monotherapy in PD

	Pros	Cons
MAO-B inhibitors (selegiline, rasagiline)	Convenient dosing, few and mild side effects	Modest symptomatic benefit
Centrally acting anticholinergic drugs (procyclidine)	Inexpensive	Many side effects Tremor responds well other symptoms don't
Dopamine agonists (cabergoline, pramipexole, etc.)	Less likely dyskinesias compared to levodopa	Less effective than levodopa
Levodopa	Most effective, easy titration, generics are cheap	Levodopa-induced dyskinesias

Therapeutic considerations in PD

- Early phase: selegiline or rasagiline or DA agonists
- Start of substitution should be prolonged as late as possible
- Anticholinergic drugs: only in the tremor dominant form and in drug-induced Parkinson's syndrome

Alzheimer's disease

- Dementia (DSM-5: a neurocognitive disorder): long term and gradual decrease of the cognitive functions (thinking, memory). Eventually it also affects emotions (affective problems) and motivations
- Alzheimer's dementia is common – appr. 60% of dementia cases. Short term memory is impaired first.
- Possible reasons / risk factors:
  - Genetic heritability from 49% to 79%
  - Head injury
  - Depression
  - Hypertension

Symptoms of Alzheimer's disease

- Short term memory loss
- Apraxia (problems with motoric execution, e.g. dressing up)
- Language problems (fewer and fewer words, fluency problem)
- Later motoric problems, long term memory impairement
- Behavioral changes (aggression, irritability, mood fluctuations)
- Extreme apathy, no movement eventually

Theories of Alzheimer's disease

- Genetic reason
- Cholinergic theory - decreased ACh in the hypocampus
- Amyloid theory – pathological β-amyloid accumulation – amyloid related protein activates „death receptors"
- Tau-hypothesis – death pathway activation, microtubule disintegration, cytoskeleton collapse
- Disruption of biometal homeostasis – aluminum (highly questioned theory)

Treatment of Alzheimer's disease

- Acetylcholinesterase inhibitors
  - Rivastigmine
  - Donepezil
  - Galantamine
- NMDA antagonist
  - Memantine
- Other treatment options (clinical studies)
  - Amyloid vaccination – the immune system would recognize β-amyloid
  - Amyloid antibodies - bapineuzumab

Huntington's chorea

- Inherited disease – autosomal dominant
- Complex extrapyramidal motoric and behavioral changes
  - Choreoathetoid dyskinesias (probably due to the degeneration of striatonigral GABA-ergic pathway)
  - Cognitive and conative impairment (decision making, abstract thinking, initiation of proper behavior, inhibition of improper behavior are impaired, personaliy change, dementia)
- Treatment:
  - GABA-ergic drugs like baclofen or benzodiazepines
  - Tetrabenazine (monoamine depletor)
  - Antipsychotics (e.g. haloperidol, tiapride)

Vascular dementia

- Also called: vascular cognitive impairment, multi-infarct dementia (MID)
- Cause: multiple microstrokes
- Symptoms: impaired cognition (memory, learning, abstraction), motoric problems (bradykinesia), sometimes dysarthria, aphasia
- Treatment:
  - Similar to Alzheimer's
  - Gingko biloba
  - Nootropic agents ("brain brighteners"): piracetam, vinpocetine, nicergoline

Wilson's disease

- Genetic disease – autosomal recessive
- Copper accumulates in the body
- Mainly affected organs: liver and brain
  - Neurologic symptoms: tremor, dysarthria, rigidity (Parkinson-like symptos); personality changes; cognitive impairment (frontal lobe symptoms); seizures; psychosis
  - Liver: portal hypertension, esophagus varices, cirrhosis, hepatocellular carcinoma
- Treatment: D-penicillamine, trientine (chelators); Zn

Amyotrophic lateralsclerosis (ALS)

- Motoneuron degeneration – both central and peripheral
- Mixed spastic and paralytic paresis progressively (rapid, aggressive disease, survival 2-4 years)
- Treatment: riluzole – Na^+-channel blocker, survival increase 2 months

Spinal muscular atrophy - SMA

- Genetic disease – disfunction of smn (survival motoneuron) gene
- Symptoms: gradual, progressive muscular atrophy, muscle weakness becuase of the death of motoneurons – neck, trunk, extremities, respiratory muscles in the end
- Prognosis – depending on the type (4 types)– from childhood to adulthood

Treatment of SMA

- Therapy:
  - nusinersen (Spinraza®)
    - siRNS, antisense oligonucleotide (ASO), increases the proportion of exon 7 inclusion in survival motor neuron 2 (SMN2) messenger ribonucleic acid (mRNA) transcripts by binding to an intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-messenger ribonucleic acid (pre-mRNA). By binding, the ASO displaces splicing factors, which normally suppress splicing. Displacement of these factors leads to retention of exon 7 in the SMN2 mRNA and hence when SMN2 mRNA is produced, it can be translated into the functional full length SMN protein.
    - injection, every 4 months after an initial loading
    - Adverse effects: headache, nausea, back pain
  - onasemnogene-abeparvovec (Zolgensma®)
    - adeno-associated viral vector-based gene therapy (one of the so-called ”Advanced Therapy Medicinal Product (ATMP)”)
    - human SMN gene inclusion
    - Adverse effects: severe acute hepatotoxicity