The Diflunisal Trial

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Familial Amyloid Polyneuropathy

Basis: Misfolding of variant transthyretin (TTR)

Factory: Liver, eye, brain

Genetics: Autosomal dominant inheritance

Features: Sensory and motor peripheral neuropathy
Autonomic neuropathy
orthostasis
GI dysmotility
Infiltrative cardiomyopathy
Renal disease

Outcome: Death 7-15 years after presentation
Transthyretin (TTR)

Trans = transport
thy = thyroid hormone
retin = retinoic acid
Gene therapy: Liver Transplantation

- 1990 Karolinska Institute, Sweden
- 1991 Deaconess Hospital, Boston MA
- FAP World Transplant Registry: 20-year experience
  - 1789 OLT (FAPWTR: 31 December 2009)
  - 92.3% 5-year survival (Am J Transplant 2007)
  - 46 variant TTR genotypes
  - 19 OLT + OHT
Post Liver Transplant Problems

Progressive heart thickening
  1997 Dubrey et al (Transplantation 64:74-80)
    • 45% increasing LVH – non-V30M
  2002 Olofsson et al (Transplantation)
    • V30M ATTR patients

Ocular disease

Arrhythmias

Peripheral neuropathy
Transthyretin (TTR)
Diflunisal (Dolobid) IND 68092

- modified aspirin-like chemical
- Non-Steroid Anti-Inflammatory Drug (NSAID)
- High blood concentrations and minimal side effects
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Genetics: Autosomal dominant inheritance
> 100 variant TTR genes – destabilize tetramer

Features: Sensory and motor peripheral neuropathy
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Peripheral Neuropathy in FAP

Disease model: Peripheral neuropathy in diabetes mellitus
  Microscopic tissue changes
  Peripheral & autonomic neuropathies

Neurologic Impairment Score + 7 (NIS+7): Peter Dyck, Mayo Clinic
  Nerve Conduction Velocities
  Computer driven Sensory Testing
  Muscle strength & Reflex Assessment
  Heart rate variation with deep breathing
Clinical Trials

• Autosomal dominant genetics = family disease

• Participating in a clinical trial
  • Close follow up by disease experts
  • Careful monitoring of drug effects & side-effects
  • Collection and analysis of data → approved new Rx
CONCLUSIONS

• Get tested -- know your genetics

• Be part of the solution → participate in trials

• Encourage your physicians to contact FAP experts and refer to amyloid programs