

Are pharmacological treatments for familial amyloid polyneuropathy effective and safe? A Cochrane Review summary with commentary

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Abstract.

BACKGROUND: Familial amyloid polyneuropathies (FAPs) are a group of rare autosomal dominant transmitted disorders that can progressively lead to disability from neuropathy, autonomic failure and other system involvement.

OBJECTIVE: The aim of this commentary is to discuss Cochrane evidence on the efficacy and safety of disease-modifying drugs (DMDs) for the treatment of FAPs from a rehabilitation perspective.

METHODS: To summarize and discuss from a rehabilitation perspective the published Cochrane Review “Pharmacological treatment for familial amyloid polyneuropathy” by Magrinelli et al.

RESULTS: This Cochrane review included 4 randomized controlled trials (RCTs) involving 655 adults with FAP. These four trials compared four different DMDs with placebo. The Cochrane Systematic Review reported that current evidence is limited.

CONCLUSIONS: FAPs are a group of chronic disabling conditions in which a multidisciplinary approach, including an adequate rehabilitation programme along with a long-term effective pharmacological therapy, should always be envisaged.

Keywords: Familial amyloid polyneuropathies, disease-modifying drugs, rehabilitation, disability

The aim of this commentary is to discuss the Cochrane Systematic Review “Pharmacological

treatment for familial amyloid polyneuropathy” (Magrinelli et al., 2020)^a, published under the direct supervision of Cochrane Neuromuscular Group, from a rehabilitation perspective. This Cochrane Corner is produced in agreement with NeuroRehabilitation by Cochrane Rehabilitation.

^aThis summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2020, Issue 4, Art. No.: CD012395, DOI: 10.1002/14651858.CD012395.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review. The views expressed in the summary with commentary are those of the Cochrane Corner author and do not represent the Cochrane Library or Wiley.

1. Background

Familial amyloid polyneuropathies (FAPs) are a group of autosomal dominant transmitted disorders,

in which neuropathy is caused by deposits of amyloid fibrils. The most common form of FAP is due to a mutation of transthyretin (TTR). TTR-FAP is usually characterized by a length-dependent sensorimotor polyneuropathy leading to wheelchair confinement, often associated with autonomic involvement. Disease-modifying drugs (DMDs) for TTR-FAP have recently become available; however, evidence of their efficacy and safety is limited.

Rehabilitation as the “medicine of functioning” is described by the International Classification of Functioning, Disability and Health (ICF) (Gutenbrunner et al., 2011). It has been recently considered as the key health strategy of the 21st century addressing all chronic disabling conditions (Gimigliano et al., 2017).

Information on the efficacy and safety of the DMDs on disability progression in people with FAPs would be of major importance for rehabilitation professionals to plan an adequate individualized rehabilitative programme (IRP).

Pharmacological treatment for familial amyloid polyneuropathy. (Magrinelli F, Fabrizi GM, Santoro L, Manganelli F, Zanette G, Cavallaro T, Tamburin S, 2020)

2. Objective

The aim of this Cochrane Systematic Review was to assess the efficacy and safety of DMDs for FAPs.

2.1. What was studied and methods

The population addressed in this review included adults with a genetically confirmed FAP. The interventions studied were any DMDs for FAPs in any dose and by any route. The intervention was compared to placebo, no intervention, or any other active comparator. The primary outcome studied was disability due to FAP progression; secondary outcomes were severity of peripheral neuropathy, quality of life (QoL), severity of depression, number of people who died during the trial, and adverse events.

A systematic search of randomized controlled trials (RCTs) and quasi-RCTs was conducted on November 18, 2019.

3. Results

This Cochrane review included four RCTs involving 655 adults all with TTR-FAP. Three of the four

trials were funded by pharmaceutical companies.

The review shows that:

- One RCT (128 people) compared ‘tafamidis’ (amyloid kinetic stabiliser) with placebo. Disability was not explored. After 18 months, ‘tafamidis’ may slightly reduce the severity of peripheral neuropathy (low-certainty evidence), however, it was uncertain whether it improved QoL, mortality, and adverse events (very low-certainty evidence).
- One RCT (130 people) compared ‘diflunisal’ (amyloid kinetic stabiliser) with placebo. After 2 years, diflunisal may slightly reduce disability due to FAP progression and the severity of peripheral neuropathy (low-certainty evidence), however, it was uncertain whether it improved QoL, mortality, and adverse events (very low-certainty evidence).
- One RCT (225 people) compared ‘patisiran’ (gene therapy with small interfering RNA) with placebo. After 18 months, patisiran probably decreased disability due to FAP progression and slightly reduced the severity of peripheral neuropathy (moderate certainty evidence), it may decrease QoL slightly less than placebo, and may make little or no difference in mortality, and adverse events (low-certainty evidence).
- One RCT (172 people) compared ‘inotersen’ (gene therapy with antisense oligonucleotide) with placebo. Disability was not explored. After about 16 months, inotersen probably reduced progression of peripheral neuropathy (moderate-certainty evidence), and may make little or no difference in QoL, mortality, and adverse events (low certainty evidence).

None of the trials explored the severity of depression.

4. Conclusions

The authors concluded that all four drugs may be effective in the treatment of people with TTR-FAP, even though all trials had limited sample sizes, and the quality of the current evidence is moderate to very low. Long-term follow-up studies might help to define which drugs are more effective and safe in the long term. Further independent studies could be included in future interactions of this Intervention Review and eventually in a Multiple Treatments Network Analysis for indirect comparisons.

4.1. Implications for practice in neurorehabilitation

This Cochrane Review studied the current evidence on the effectiveness and safety of the available DMDs for reducing disability progression in people with FAPs. As FAPs are a group of chronic disabling conditions, a multidisciplinary approach considering an IRP along with the long-term pharmacological therapy, should always be envisaged. It would be of great interest for rehabilitation professionals if future trials were based on this multidisciplinary approach and investigate the combined effectiveness of drugs and rehabilitation using ICF based outcome measures, including body functions (weakness, pain and fatigue), activity limitation and participation restriction.

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Conflict of interest

The author declares no conflicts of interest.

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