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The Swedish open-label diflunisal trial (DFNS01) on hereditary transthyretin amyloidosis and the impact of amyloid fibril composition

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Background

The non-steroidal anti-inflammatory drug diflunisal has been shown to stabilize transthyretin (TTR) and thereby prevent amyloid fibril formation. After the international randomized, double blind, placebo-controlled diflunisal trial [1] was closed for enrolment in 2011, the Swedish DFNS01 study was started to continue monitoring the effect of diflunisal in patients with hereditary transthyretin (ATTRm) amyloidosis. Since TTR amyloid fibril composition has been shown to be important for disease outcome [2], amyloid fibril type was taken into account when analysing the study results.

Material and methods

DFNS01 was a 24-month open-label observational study designed to monitor the effect of diflunisal 500 mg daily in ATTRm amyloidosis. It was open for enrolment from July 2011 to the publication of the controlled diflunisal trial. Primary outcome measure was changes in the Kumamoto scale [3], and secondary outcome measures were changes in nutritional status (modified body mass index (mBMI), p-albumin × BMI) [4], cardiac function (septal thickness, p-proBNP) and safety follow-up blood tests (b-haemoglobin, b-platelets, p-creatinine, p-liver enzymes). Evaluations were performed yearly. Amyloid fibril type was established from abdominal fat pad biopsies with Western blot analyses [2]. Late disease onset was defined as onset ≥50 years of age.

Results

Fifty-four patients were included and their baseline characteristics are shown in Table 1. Of those included, 14 (26%) had received diflunisal prior to inclusion in DFNS01 with a median pre-study treatment of 2 (full range 0.1–4) years. Seventeen (31%) of the patients had completed the 24-month study follow-up, whereas 37 (69%) had dropped out after a median duration of 10.8 (0.4–21.8) months. Thirty-four patients had completed 12 months. The main reasons for early termination were study closure (40%), liver transplantation (24%), and side effects (19%). Of the nine

Table 1. Baseline patient characteristics.

	Completers ($n = 17$)	Non-completers ($n = 37$)	p Value
Age at inclusion	69 (31–82) years	67 (30–81) years	.06
Duration of disease	2.2 (0–10) years	3.2 (0–11) years	.66
Late disease onset	60%	40%	.02
Male sex	45%	55%	.32
TTR V30M mutation	96%	100%	.31
Full-length amyloid fibrils	42%	58%	<.01
Total Kumamoto score	13 (1–44)	10 (0–36)	.23
Cardiac septum thickness	16 (9–26) mm	13 (8–24) mm	<.01
Modified BMI	1019 (651–1445)	972 (425–1494)	.66
Normal ECG	35%	65%	.05
P-proBNP	643 (30–9622) ng/L	161 (22–6459) ng/L	.01
B-haemoglobin	143 (115–165) g/L	144 (121–160) g/L	.52
B-platelets	198 (127–324) 10^9/L	213 (145–331) 10^9/L	.08
P-creatinine	68 (49–143) µmol/L	75 (41–151) µmol/L	.06
P-AST	0.5 (0.3–1.0) µkat/L	0.5 (0.3–1.4) µkat/L	.14
P-ALT	0.4 (0.1–1.1) µkat/L	0.4 (0.1–2.5) µkat/L	.84

TTR: transthyretin; BMI: body mass index; BNP: brain natriuretic peptide; AST: aspartate aminotransferase; ALT: alanine aminotransferase. Data shown are medians (full range). p Values <.05 were considered statistically significant.

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transplanted patients, eight (89%) were males, eight (89%) had full-length amyloid fibrils only and seven (78%) had an early disease onset. The most frequent side effects were dyspepsia (12%), diarrhoea (9%) and increased p-creatinine (7%). For patients who had completed the study protocol, total Kumamoto scores had remained stable (median score 13 vs. 16 vs. 17.5, $p = .21$), as had the sub-scores for sensory neuropathy, autonomic neuropathy and organ dysfunction. However, motor neuropathy scores had increased slightly over time (0 vs. 2.5 vs. 4.5, $p=.02$). No significant changes were found for mBMI (1028 vs. 918 vs. 982, $p=.06$) or p-proBNP (532 vs. 412 vs. 457 ng/l, $p=.19$), whereas cardiac septum thickness had increased over time (16.5 vs. 16.5 vs. 18 mm, $p=.01$). No significant changes were found for those who had completed 12 months. Safety follow-up blood tests were stable at both the 12 and 24 month follow-ups. Among the seven patients who had completed the DFNS01 protocol, and received pre-study treatment with diflunisal, no significant changes were found for any of the outcome measures. Amyloid fibril type had been established in 42 (79%) patients, and 16 (38%) were of type A (fibrils consisting of both full-length and fragmented TTR). Type A patients were all late-onset cases ($\geq$50 years) and had a significantly higher pro-BNP, total Kumamoto score and septal thickness than type B patients at inclusion. Sub-group analyses showed no significant change over time in any of the outcome measures, neither for type A nor for type B patients.

Discussion and conclusions

Although limited by high dropout rates, mainly due to liver transplantation and study closure, the DFNS01 trial supports the safety and efficacy of diflunisal for ATTRm amyloidosis, and the results are in line with the previous placebo-controlled trial. Total Kumamoto scores and nutritional status remained stable, however, motor neuropathy scores and cardiac septum thickness increased significantly during the study, which suggests that complete disease stabilization is not achieved on group level. No obvious difference in outcome was noted with regard to amyloid fibril type, but the number of patients was low. Further studies are needed to evaluate the long-term effect of diflunisal and whether all sub-groups of patients have the same beneficial treatment effect.

Disclosure statement

No potential conflict of interest was reported by the authors.

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