

Regression of amyloid load in subcutaneous fat tissue of hereditary transthyretin amyloidosis patients during treatment with patisiran

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INTRODUCTION

Patisiran, a small interfering RNA, improves neuropathy and cardiac parameters in hereditary ATTR (ATTRv) amyloidosis¹⁻³. Reductions in extracellular volume on cardiac magnetic resonance imaging and cardiac tracer uptake on bone scintigraphy in patients receiving patisiran suggest amyloid regression^{4,5}. However, evidence confirming amyloid regression is lacking.

OBJECTIVE

This study aims to evaluate if amyloid load in abdominal fat tissue aspirates changes during treatment with patisiran.

METHOD

All ATTRv amyloidosis patients treated with patisiran at the University Medical Center of Groningen (UMCG), the Netherlands, were evaluated for eligibility in this study. Patients that did not have a subcutaneous fat tissue aspirate performed within one year before initiation of patisiran or during follow-up, were excluded from analysis. Fat tissue aspirates were stained with Congo red (CR) as part of routine care and scored semi-quantitatively from 0 to 4+ (Figure 1). CR-scores before and after initiation of patisiran were extracted from the patient files and compared using the Wilcoxon signed-rank test. A one-point decrease in CR-score was utilized to generate Kaplan-Meier curves for patients with varying levels of serum transthyretin (TTR) reduction. Only patients with a baseline CR-score above zero, were included in this analysis, as only these patients can experience a decrease in CR-score. The log-rank test was used to detect differences between the curves.

RESULTS

Of the 66 ATTRv amyloidosis patients that are currently being or have been treated with patisiran at the UMCG, 41 patients were included in this ongoing observational study, patient characteristics at baseline are shown in Table 1. Median serum TTR reduction was 79%. Prior to initiation of patisiran, CR-score significantly increased with a median change of +1 (p=.002). Within the first year of treatment with patisiran, median change in CR-score was 0 (p=.127). Between one and two years after the initiation of patisiran, CR-score decreased significantly. Median change in CR-score was -1 (p=.011*). Between baseline and the longest individual follow-up, median change in CR-score was -1 (p=.002*) (Figure 2).

Congo red score decreased by at least one point in 56% of patients after a median of 36 months. No differences were observed in the decrease in CR-score between patients with different levels of serum TTR reduction (p=.291) (Figure 3).

CONCLUSION

- CR-score decreases after a median of 36 months of treatment with patisiran in ATTRv amyloidosis patients
- First study to provide evidence for regression of amyloid in tissue
- Analyses relating serum TTR reduction and other predictors of amyloid regression did not reveal any correlations but are ongoing

REFERENCES

1. Adams et al, 2018, *N Eng J Med* 2. Solomon et al, 2019, *Circulation* 3. Maurer et al, 2023, *N Engl J Med* 4. Fontana et al, 2020, *JACC Cardiovasc Imaging* 5. Tingen et al, 2024, *Eur J Nucl Med Mol Imaging*.

ABBREVIATIONS

ATTRv = hereditary transthyretin; UMCG = University Medical Center Groningen; CR = Congo red; TTR = transthyretin; IQR = interquartile range; FU = follow-up

Table 1. Patient characteristics at baseline.

Characteristic	Total (n=41)
Age (years)	62 [50-71]
Male	26 (63%)
TTR reduction (%)	79 [67-87]
Laboratory tests	
NT-proBNP (ng/L)	216 [75-927]
Hs-cTnT (ng/L)	14 [8-29]
Mutation	
p.(Val50Met)	22 (54%)
p.(Val91Ala)	5 (12%)
p.(Val142Ile)	5 (12%)
p.(Glu109Lys)	3 (7%)
Other	6 (15%)

Variables are presented as median [IQR] or n (%)

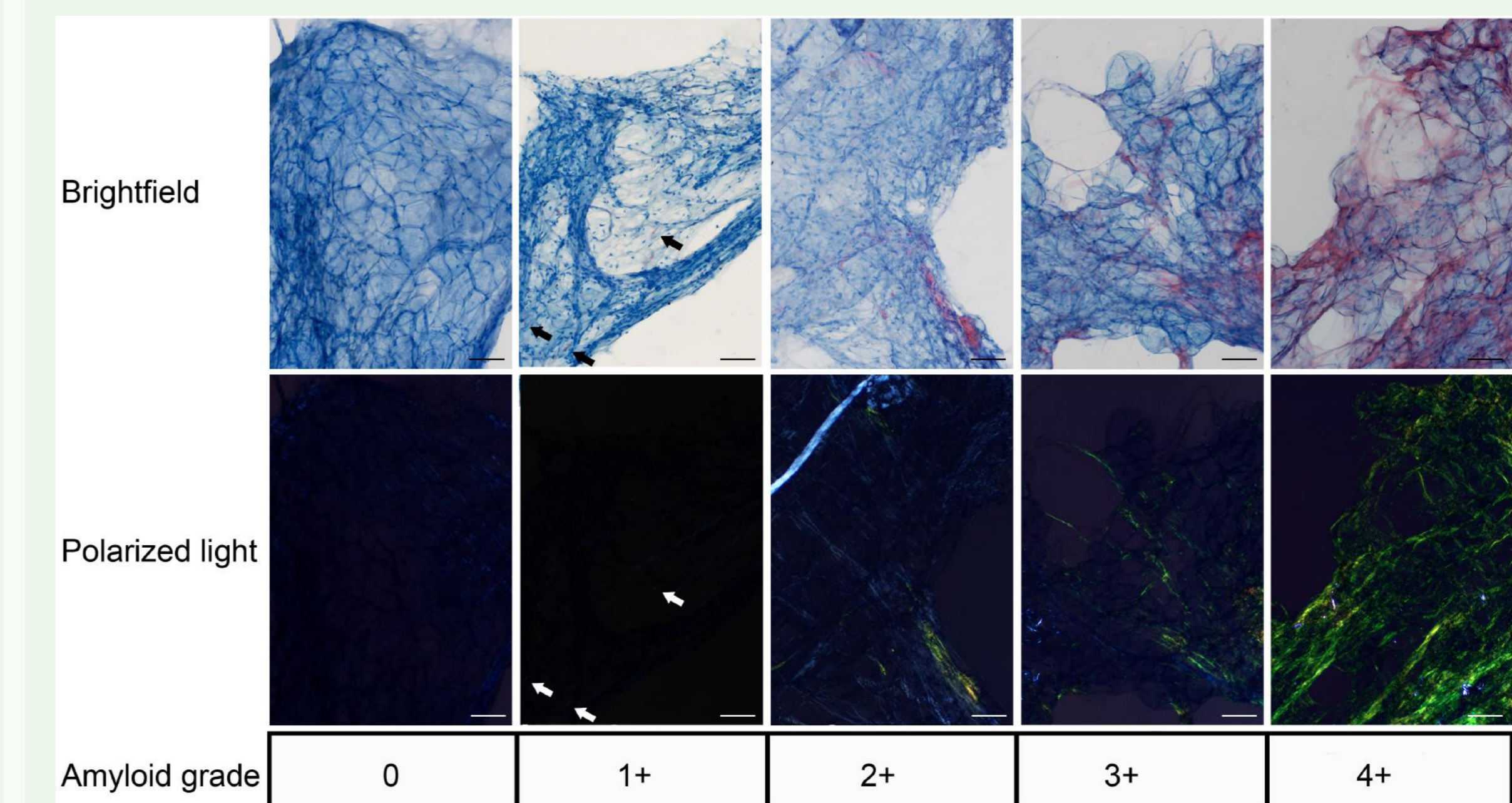


Figure 1. Examples of CR-scores in brightfield and polarized light microscopy.

Arrows indicate CR positive regions. Bar = 100 μm in all images.

Δ CR-score during follow-up in patients treated with patisiran

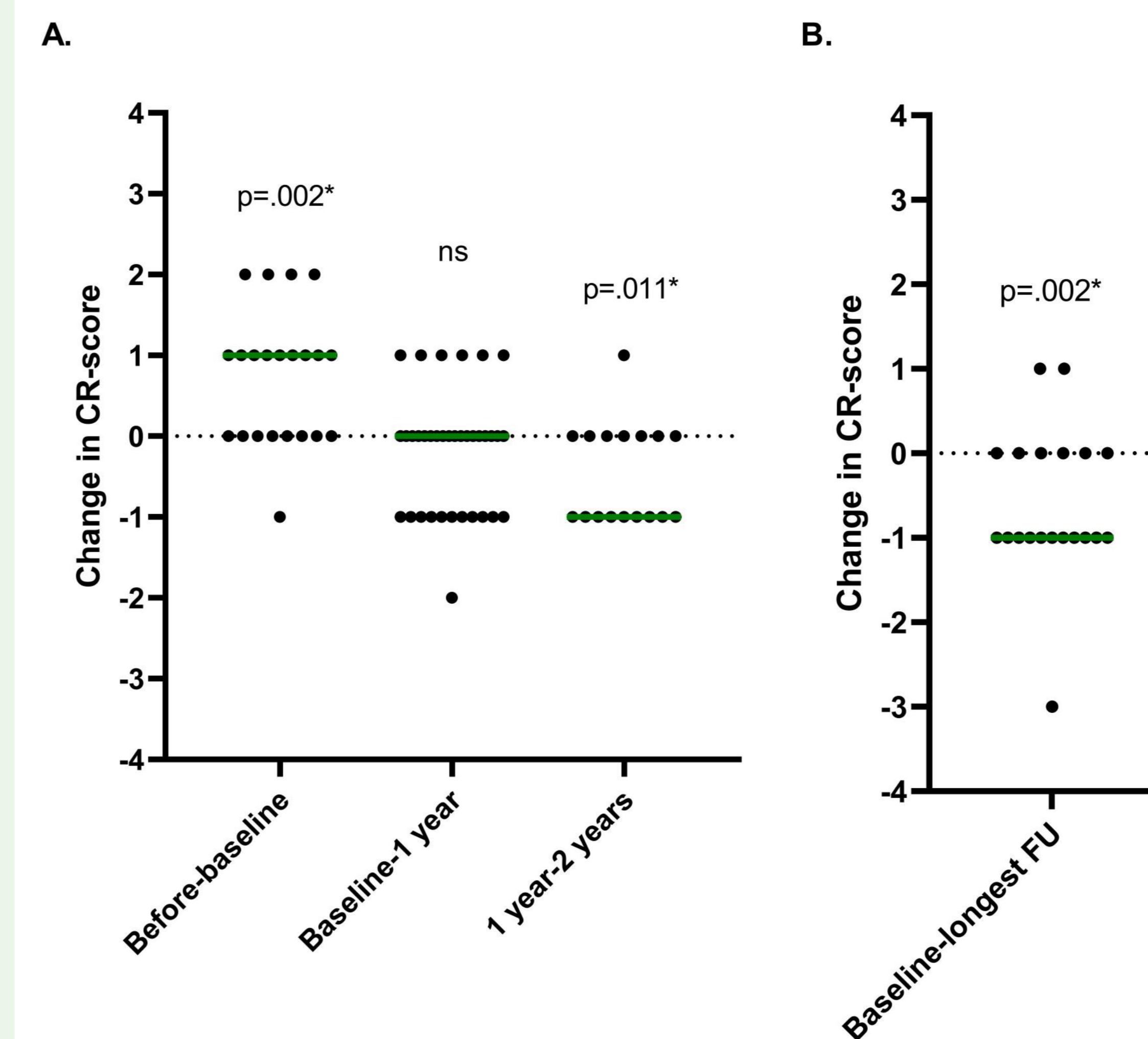


Figure 2. Change in CR-score in subcutaneous abdominal fat tissue aspirates of patients treated with patisiran. **A.** Change between consecutive follow-up moments. **B.** Change in CR-score between baseline and the last follow-up for every individual patient.

The green horizontal line represents the group median.

Decrease in CR-score in patients treated with patisiran

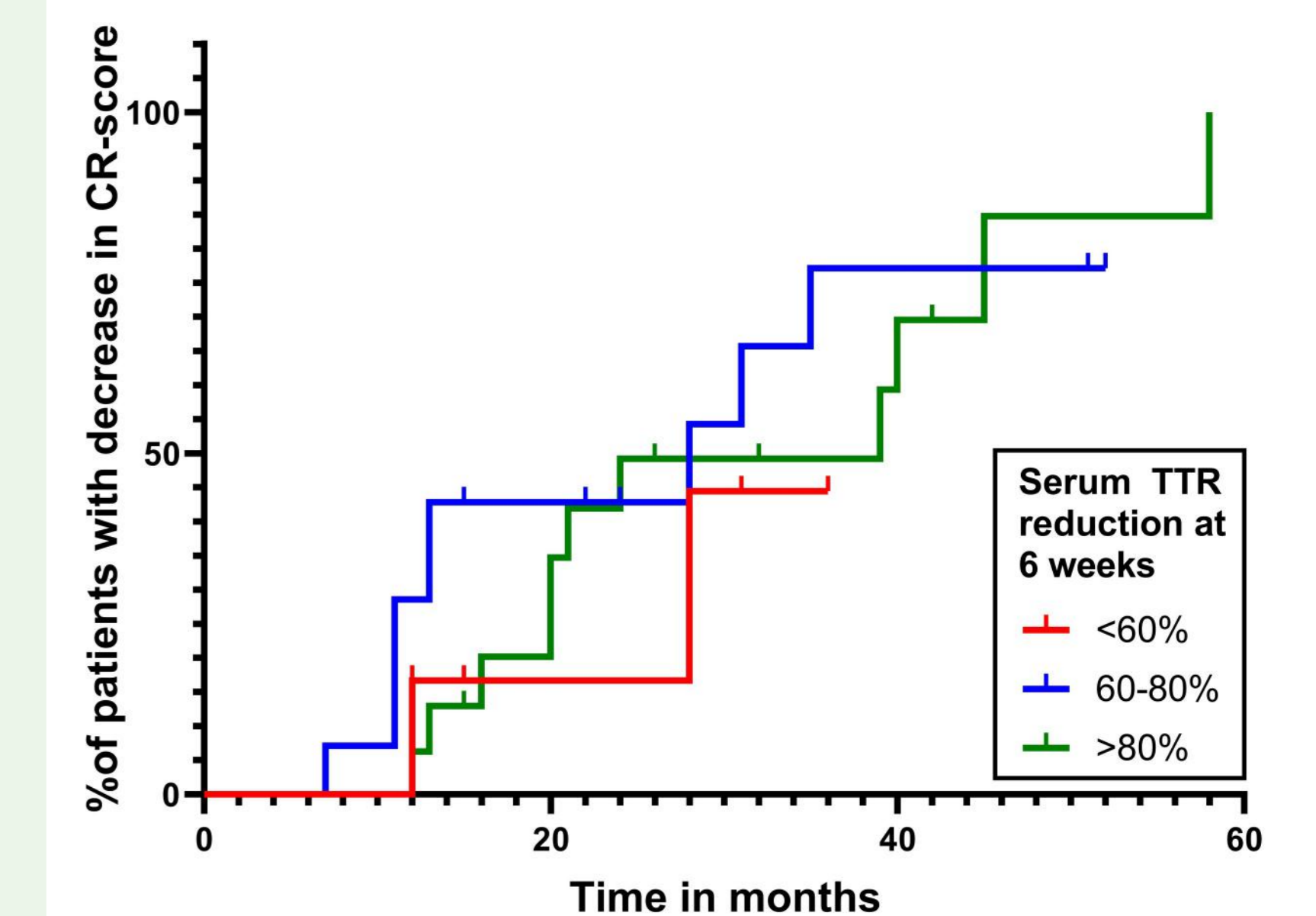


Figure 3. Kaplan-Meier curves of patients with varying levels of serum TTR reduction. The endpoint is a decrease in CR-score of at least 1 point. The numbers of patients at start and later who had the potential to show a decrease in CR-score are shown at the bottom.

