NASH Progression Rates Based on Fibrosis and Inflammation (NAS): A Paired Biopsy Analysis From a Natural History Cohort in the US

Tapper E[1], Fishman J[2], Mospan AR[3], Morris HL[3], Munoz B[3], Newsome P[4], Loomba R[5] on behalf of TARGET-NASH Investigators

[1]University of Michigan, Ann Arbor, MI; [2]Madrigal Pharmaceuticals, Conshohocken, PA; [3]Target RWE, Durham, NC; [4]National Institute for Health Research Birmingham Biomedical Research Centre at University Hospitals Birmingham NHS Foundation Trust and the Centre for Liver and Gastrointestinal Research, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK; [5]NAFLD Research Center, Division of Gastroenterology, University of California at San Diego, La Jolla, CA.

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BACKGROUND

- Disease progression in nonalcoholic steatohepatitis (NASH) is assessed by:
  - Progression of fibrosis (from F0 to F4 [most severe/cirrhosis])
  - Inflammation (evaluated via the nonalcoholic fatty liver disease activity score [NAS])[1,2]
- Data on disease progression are essential to support state transition probabilities in economic models
- However, real-world data are limited regarding fibrosis and lacking regarding inflammation (NAS) in patients with NASH

OBJECTIVE

- To estimate NASH progression in a natural history cohort stratified by both baseline fibrosis stage and inflammation (NAS)

METHODS

- Data from patients enrolled in a longitudinal observational cohort study (TARGET-NASH [ClinicalTrials.gov identifier, NCT02815891]) with biopsy-confirmed NASH, paired liver biopsies, and NAS were used to determine the transition probability of NAS and conditional probability of fibrosis progression
- Multinomial logistic regression was adapted to estimate the transition probabilities
- NAS ≥4, an inclusion criterion in NASH clinical trials, was examined categorically

RESULTS

- In total, 152 patients were included in this analysis
  - The majority of patients were White (n=136; 89.5%) and female (n=93; 61.2%)
  - Mean age at enrollment was 55.5 years (standard deviation [SD], 11.72)
  - Mean body mass index (BMI) at enrollment was 33.0 kg/m^2 (SD, 6.40) with most patients (n=99/150) below the severe obesity category (BMI ≤35 kg/m^2)
- On average, the time between the paired liver biopsies was 45.8 months (SD, 44.83)
  - 23.0% (n=35) of patients had the biopsies within 1 year of each other, 20.4% (n=31) had the biopsies 1-2 years apart, and 56.6% (n=86) had the biopsies 2+ years apart
- At 1st biopsy, 46.7% (n=71) of patients had a NAS <4 and 53.3% (n=81) had a NAS ≥4
- Regardless of initial NAS, fibrosis stage more likely remained the same or increased versus decreased: 83.1% (n=59) of patients with NAS <4 (**Table 1**) and 79.0% (n=64) of patients with NAS ≥4 (**Table 2**)
- The annual transition probability in the NAS <4 group (n=27) to NAS ≥4 was 0.29 (95% confidence interval [CI]: 0.10-0.47); in the NAS ≥4 group (n=44), the probability of transitioning to NAS <4 was 0.37 (95% CI: 0.22-0.53) (**Table 3**)

Table 1. 1-year fibrosis transition probabilities among patients with NAS <4 at 1st biopsy

	Fibrosis Progression			
Fibrosis stage at 1st biopsy	**Decreased**	**Same**	**Increased**	**Total**
F0	0 (n=0)	0.2 (n=3)	0.8 (n=10)	13
F1	0.11 (n=3)	0.55 (n=12)	0.35 (n=7)	22
F2	0.44 (n=5)	0.34 (n=4)	0.22 (n=2)	11
F3	0.2 (n=4)	0.54 (n=10)	0.26 (n=4)	18
F4	0 (n=0)	1 (n=7)	0 (n=0)	7
Total	12	36	23	71

Table 2. 1-year fibrosis transition probabilities among patients with NAS ≥4 at 1st biopsy

	Fibrosis Progression			
Fibrosis stage at 1st biopsy	**Decreased**	**Same**	**Increased**	**Total**
F0	0 (n=0)	0.51 (n=1)	0.49 (n=3)	4
F1	0.06 (n=2)	0.52 (n=11)	0.42 (n=11)	24
F2	0.17 (n=3)	0.32 (n=4)	0.52 (n=8)	15
F3	0.3 (n=8)	0.53 (n=12)	0.16 (n=4)	24
F4	0 (n=4)	1 (n=10)	0 (n=0)	14
Total	17	38	26	81

Table 3. NAS transition probabilities among patients with NAS at 1st and 2nd biopsies

	NAS at 2nd Biopsy		
NAS at 1st biopsy	**<4**	**≥4**	**Total**
<4	0.71 95% CI: 0.53-0.90 (n=18)	0.29 95% CI: 0.10-0.47 (n=9)	27
≥4	0.37 95% CI: 0.22-0.53 (n=15)	0.63 95% CI: 0.47-0.78 (n=29)	44
Total	33	38	71

CONCLUSIONS

- Most patients with NASH were unlikely to achieve fibrosis improvement within 1 year regardless of initial NAS (<4 or ≥4)
- NAS transition probabilities reflected annual changes in fibrosis stage
- Calculating NAS is feasible for inclusion in economic models and its inclusion will enable modeling of earlier disease progression in NASH

LIMITATIONS

- This is a small retrospective study due to the requirement of 2 paired biopsies. Looking at changes in fibrosis as a function of changes in NAS in a larger cohort would validate the relationship between the two.
- The model assumes transition is linear, but this is unlikely in practice. The exact time of transition was not observed, transitions may have occurred outside the biopsy dates and a transition between contiguous states (fibrosis stages) is not instantaneous. Therefore, this approach focused on the underlying progression across states rather than the observed progressions

REFERENCES

1. Kleiner DE, et al. *Hepatology*. 2005;41:1313-21.
2. Leoni S, et al. *World J Gastroenterol*. 2018;24:3361-73

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