A Markov model unveiling the impact of Resmetirom on the natural history of MASLD patients with baseline significant or severe liver fibrosis

Grazia Pennisi1, Gabriele Di Maria2, Marco Enea3, Marco Vaccaro3, Carlo Ciccioli1, Ciro Celsa1, Giuseppe Infantino1, Adele Tulone1, Vito Di Marco1, Calogero Camma1, Salvatore Petta1

1Section of Gastroenterology and Hepatology, Dipartimento Di Promozione Della Salute, Materno Infantile, Medicina Interna e Specialistica Di Eccellenza (PROMISE), University of Palermo, Italy, Palermo, Italy, 2Dipartimento Di Promozione Della Salute, Materno Infantile, Medicina Interna e Specialistica Di Eccellenza (PROMISE), University of Palermo, Italy, Palermo, Italy, 3Dipartimento di Scienze Economiche, Aziendali e Statistiche, University of Palermo, 90133 Palermo, Italy, Palermo, Italy

Email: graziapennisi901@gmail.com

Background and Aims: The MAESTRO-NASH phase 3 trial reported that 52-week treatment of Resmetirom is effective in improving fibrosis and MASH in patients with metabolic-dysfunction associated steatotic liver disease (MASLD) with F2 or F3 fibrosis, while data on the impact on 5-year and long-term clinical outcomes are still lacking. Moreover, data about the full spectrum of the natural history of MASLD patients with F2 or F3 fibrosis are scarce and fragmentary. We simulated the transition probabilities of disease progression in MASLD patients with F2 or F3 fibrosis, and the effect of Resmetirom treatment on clinical outcomes.

Method: Data from 12 studies and individual sources on MASLD subjects formed transition matrices for fibrosis stages and complications, defined as compensated (CC) and decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) and mortality - liver-related mortality (LR-M), cardiovascular mortality (CV-M) and extra-hepatic cancer mortality (EHC-M). Markov model was developed to depict the F2 and F3 fibrosis stage progression towards the complications and to evaluate the effect of Resmetirom treatment on the natural history of MASLD.

Results: We estimated the five-year probability of Resmetirom-treated and untreated MASLD patients with baseline F2 fibrosis of developing CC (5.16 vs 6.82, respectively), DC (0.25 vs 0.3, respectively), HCC (0.25 vs 0.32, respectively) and mortality (0.15 vs 0.16 for LR-M; 1.02 vs 1.1 for CV-M; 1.07 vs 1.2 for EHC-M, respectively). Similarly, we estimated the five-year probability of Resmetirom-treated and untreated MASLD patients with baseline F3 fibrosis of developing CC (17.12
vs 21.34, respectively), DC (1.1 vs 1.47, respectively), HCC (1.21 vs 1.73, respectively) and mortality (0.59 vs 0.91 for LR-M, 1.92 vs 2.14 for CV-M and 1.04 vs 1.14 for EHC-M, respectively). Comparable results were obtained extending these probabilities to a lifetime horizon for both F2 and F3 MASLD patients. Sensitivity analyses considering changes in transition probabilities, treatment efficacy and treatment duration are ongoing.

**Conclusion:** Resmetirom decreases the 5-year and lifetime Markov-model estimated risk of CC, DC, HCC, and liver-related and extra-hepatic mortality in patients with MASLD and F2 or F3 fibrosis.