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Simulating the decline of HCV infected hepatocytes by mathematical modelling allows for individual tailoring of Peg-IFN+RBV therapy and for a better selection of the candidates to the new direct antiviral agents.

Background. We have already shown in a retrospective study that modelling infected cells dynamics by ALT and HCV RNA decline during the first 4 weeks of therapy warrants accurate prediction of treatment outcome and offer the possibility to compute individual treatment duration. We compared in a randomised controlled trial the duration and the efficacy of the new model tailored (MT) schedule vs the traditional Guide Line (GL). Patients and methods. 100 consecutive patients stratified by previous therapy (38 nave, 62 retreated), HCV genotype (60 G1-G4 and 40 G2-G3)and peg-IFN type (60 2a and 40 2b), randomly received GL or MT schedules. GL pts were treated 24 weeks if G2-G3 and 48 weeks if G1-G4 applying week 12 stopping rule in G1 non responders (NR). In MT patients ALT and HCV RNA were measured at day 0-2-4-7-14-21-28 to compute the number of infected cells at the end of therapy (Ieot), treatment was stopped at week 6 if computed Ieot at GL duration $>$ 5000 (NR), otherwise tailored to achieve Ieot $<$ 250. Results. Ieot could be computed in 42 (84%) MT patients, the remaining 8 pts showed ALT or HCV-RNA data that did not fit into the model, thus they were treated with GL schedules and not included in this analysis. Therapy was withdrawn/modified because of side effects in 13 (26%) MT and in 9 (18%) GL pts. Therapy was discontinued at week 6 because of NR in 11 (22%) MT pts and at week 12 in 8 (16%) GL pts. The SVR rate in those who completed therapy was 85% according to the MT (mean duration 32 weeks, range:13-56) and 82% according to the GL (mean duration 38 weeks, range:24-48). Treatment duration in SVR pts ranged between 18-55 weeks in 7 G1 pts, 13-21 weeks in 3 G2 pts and 21-56 weeks in 5 G3 pts. Mean duration for SVR of GL schedules was 21% longer in responder patients and 100% in NR. Conclusions. The prospective application of our model confirmed the wide diversification of the treatment duration required for SVR, as predicted by our previous retrospective study, and allowed in clinical practice a fine personalization of the antiviral treatment at the single patient level. Tailoring treatment to Ieot$<$250 showed SVR rates comparable to those of the standard schedules (85%

vs 82%) but with a significant reduction of non-effective and non required treatments. Use of a model computed Ieot threshold with high chance of SVR to predict treatment duration might be very helpful for decision making after a lead in phase of Peg-IFN+RBV therapy when the direct antiviral agents will be available, thus optimizing the cost-effectiveness of the new antiviral therapies.