Comments on Assessment Report: Interferon alfa and ribavirin for the treatment of mild chronic hepatitis C

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1. Given that current NICE guidelines advocate treatment of moderate/severe hepatitis the best supportive care strategy (with no antiviral treatment) in the economic model would seem largely irrelevant. Thus the key comparison is between the early treatment and watchful waiting strategies. The conclusion in the Summary that "[both] strategies are associated with acceptable cost per QALY estimates" does not provide guidance as to which strategy is preferred. The model appears to point to early treatment being the more cost-effective option, but this is not reflected in the conclusion.

2. The report reviews, in detail, eight trials in patients with mild HCV which compare IFN/PEG+RBV versus IFN/PEG monotherapy or control. In fact, the randomisation is essentially irrelevant to the key issue at hand i.e. should treatment be given immediately or deferred. Although they do provide information on the rate of SVR for patients with mild HCV, observational data from routine clinical practice (if it existed) would be equally or even more useful. It is not clear why these types of study were not considered (page 45).

3. The report lacks a thorough review of data on natural history of the infection. This information is critical to the question of whether to intervene early, more so than the RCTs (see point above). Although the available information is limited, most of it points to a lower risk of progressive liver disease than generally thought. Examples are: (1) the HPA study of transfusion recipients (BMJ 2002;324;1-6) which reported that only 10 of 117 deaths were directly related to liver disease after 10 years of infection (2) similar mortality rates by HCV status among military recruits (Ann Intern Med 2000;132;105-11) with 45 year follow-up although with small numbers (3) a low rate of abnormal ALT levels in elderly Italian persons presumed to have been infected for many years (J Med Virol 2002;67:339-44.)

4. Given the state of current knowledge, requiring questionable assumptions about the model structure and input parameters, the estimates of cost-effectiveness are necessarily subject to considerable uncertainty. It would be difficult to justify a strong recommendation for early treatment, particularly for genotypes with a lower treatment success rate.

5. The model does not take into account that treatments may well become more effective over time. This would act – presumably materially – in favour of watchful waiting.

6. It would have been helpful if the report had reviewed the evidence on whether SVR is maintained indefinitely, as the model assumes. Is there any long-term follow-up in the RCTs which shed light on this?

7. The assumption of biopsies every 3 years under seems idealistic. As described in Section 2.1.2.1 biopsy is a major barrier to treatment. Thus, in real life, the watchful waiting strategy will probably mean no intervention until the development of symptoms

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for many patients. The population impact of this strategy may lie closer to the outcomes for "best supportive care".

8. The question of whether to offer treatment to active IDUs is of key importance (page 38) and should not be considered in any recommendation.

9. Both the SHTAC model and that of Salomon conclude that the benefits of treatment are largely mediated by improved QoL rather than longer survival. Thus the utilities attached to the various states are critical. For asymptomatic patients, the effect of treatment (for most of the patient's life span) is a switch from mild disease to SVR. This implies that the relative values of the utilities in these two states are critical. In the Salomon model they are virtually identical but in the SHTAC model the utility for mild disease is considerably lower than for SVR. The reason for this is unclear; is there any disutility in asymptomatic infection other than the need for regular biopsy?

10. It is disconcerting that models developed by two expert groups (Salomon and SHTAC) arrive at quite different QALY estimates, albeit in different comparisons. The SHTAC estimates are much more optimistic than Salomon's.

11. Why would a trial of early versus deferred therapy be unethical (page 136) given the uncertainty that surrounds this question? If may not be practicable – patients may not accept randomisation, follow-up would need to be very long-term – but that is a separate issue.

12. The sensitivity of QALY estimates to the age of the cohort underlines the importance of individualised treatment strategies (discussed on page 39). Perhaps final recommendations could flag this important issue.

13. The majority of patients with HCV have a history of IDU and are therefore more likely to have higher background mortality rates than the general population. Was this taken into account in the model? It may be an important factor as a key element in watchful waiting is the percentage of patients who die before requiring treatment.

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