Clinical opinions in general medicine

The last issue of Clinical Opinions for 2004 covers four issues which hopefully will interest readers. Finlayson examines the use of statins in chronic liver disease; Howard addresses the thorny issue of when and, thornier still, when not to treat prostate cancer; MacLeod looks at how we prepare medical students for that all-important transition to house officer; and Younger and Hayes look at the best treatment options for patients co-infected with HIV and hepatitis C. As always we are keen to receive contributions from Fellows in all branches of internal medicine.

Clinical opinion: statins in liver disease

TITLE: How to use statins in patients with chronic liver disease.
KEYWORDS: Liver disease, statins.
AUTHOR: Russo MW, Jacobson IM.
JOURNAL: *Cleveland Clinic Journal of Medicine* 2004; **71**:58–62.

SUMMARY

The statins (3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors) are metabolised in the liver and consequently physicians may be reluctant to use them in patients with liver disease. Russo and Jacobson review nine reports of abnormalities of liver function tests in 23,023 patients without liver disease who were taking a variety of statins long-term. Abnormalities were restricted to asymptomatic elevations of plasma transaminase activity (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), usually occurring within 12 weeks of starting therapy, related to drug dose, and returning to normal on stopping the drug. Elevations of ALT/AST more than twice the normal upper limit occurred in 0·8% (range 0–1·8%) of patients. Accordingly, statins are regarded as safe in respect of the liver in the absence of liver disease.

The authors found that little is known regarding liver toxicity due to statins in liver disease. Hepatic fibrosis in long-term statin therapy has been reported in two cases but in neither was the possibility of pre-existing fibrosis excluded, and high blood levels have occurred in cirrhosis as would be expected in a drug undergoing first-pass metabolism in the liver.

The authors base their recommendations on statin use in liver disease on their own clinical experience, the infrequency, mild nature and reversibility of ALT/AST abnormalities in the absence of liver disease, and the lack of reports of severe liver toxicity when liver disease is present. They believe statins can be used in chronic liver disease but not in acute liver disease, that the dose should be started at the lowest therapeutic level and increased gradually, and that ALT/AST should be measured two weeks after starting or increasing the drug, monthly for three months thereafter, and then four times annually. The drug should be stopped if the ALT/AST rises to more than twice the level it was at before therapy, and another statin could be tried once the ALT/AST has returned to baseline activity.

OPINION

Most drug evaluations are carried out on young or middle-aged patients with single disease problems, whereas clinicians often face patients with multiple problems. Additionally, the liver is a major site of drug metabolism, and pharmacopoeias frequently advise particular caution in using drugs in liver disease (as is the case for statins!).[1] The result can be that patients with liver disease are denied beneficial treatments out of an excessive fear of drug toxicity or side-effects. The use of statins to prevent or treat coronary artery disease in patients with liver disease is, in fact, a situation physicians are quite likely to encounter.

Statins have an excellent long-term safety record and hepatotoxic reactions, particularly serious ones, are unusual.[2] Statins undergo first-pass metabolism in the liver, are metabolised in the cytochrome P450 system, and most (lovastatin, simvastatin, fluvastatin, atorvastatin), but not all (provastatin), are highly protein-bound (>90%) in the blood. Metabolism of these drugs is impaired when they are given with drugs such as erythromycin, diltiazem, itraconozole and cyclosporine, which inhibit the cytochrome P450 enzymes. Statin metabolism is also impaired in cirrhosis, where portal systemic shunting and impaired liver function inhibit drug metabolism and hypoalbuminaemia may limit protein binding. Toxic reactions, particularly rhabdomyolysis, are more likely to occur in these situations.

Liver disease may not increase liability to the hepatotoxic effects of drugs, but liver disease certainly reduces

the ability of patients to withstand the consequences of hepatotoxic events. Thus, the first step for the physician is to ensure that a potentially hepatotoxic drug given to such patients is being used for very good reasons. Next, while there is no sure way of predicting which patients with liver disease will develop general toxic effects when given a drug, but such effects are most likely in those with more advanced liver disease where drug metabolism is most impaired. Such patients are those with clinical (jaundice, ascites, encephalopathy, malnutrition) or laboratory (hypoalbuminuria, vitamin K-resistant prolongation of the prothrombin time) features of poor liver function. Drugs in these patients should be kept to a minimum, started at the bottom of the therapeutic range, and increased gradually to produce the desired effect at the lowest dose. Liver disease patients without these features usually tolerate drug therapy normally.

Statins are generally used to prevent or treat coronary artery disease in the long term, and the recommendations given in this paper for patients with continuing asymptomatic abnormalities of liver function tests or well-compensated liver disease (i.e. without the features itemised above), who have a good longer term prognosis, are very reasonable. Indications for treatment in these patients need be no different from patients without liver disease. By contrast, patients with advanced cirrhosis do not usually have hyperlipidaemia and have a poor long-term prognosis, and the risks of treatment are hardly justified. However, specialist advice should be sought for those with marked hyperlipaemia (usually due to cholestatic diseases such as primary biliary cirrhosis) who are likely to be suitable for liver transplantation in due course. Statins have been used safely after liver transplantation, but it is important in this circumstance that statins and cyclosporin together can predispose to severe myositis and rhabdomyolytis.[1]

Acute liver disease is generally active (indicated by high plasma ALT/AST activity) and usually self-limiting, and acute-on-chronic diseases (such as autoimmune hepatitis or alcoholic hepatitis) are treated to bring them under control. Russo and Jacobson recommend that where statins are indicated in such patients, they should be given after recovery. To this one can only say 'Amen.'

REFERENCES

1 Lipid regularity drugs. *British National Formulary 2002*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2002; Vol 44 (Section 2):12, 128–31.
2 Parra JL, Reddy KR. Hepatotoxicity of hypolipidemic drugs. *Clin Liver Dis* 2003; **7(2):**415–33.

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Clinical opinion: natural history of early localised prostate cancer

TITLE: Natural history of early, localized prostate cancer.
KEYWORDS: Prostate cancer, survival, treatment.
AUTHORS: Johansson JE, Andrén O, Andersson S-O *et al.*
JOURNAL: *JAMA* 2004; **291:**2713–19.

SUMMARY

This is probably the largest population-based cohort study of patients with prostate cancer managed by a 'watchful waiting' programme that has ever been published. It certainly has the longest and most complete follow-up. Between 1977 and 1984, 654 new cases of prostate cancer were diagnosed in a well-defined area of central Sweden. Of these, 223 patients had localised disease and fulfilled the criteria used to follow the policy then offered of so-called 'watchful waiting'. Sixty-six per cent of these patients had well-differentiated tumours and only 4% were poorly differentiated. Progression was defined as development of T3 disease or metastases. Eighty per cent of patients were rebiopsied.

At the time of analysis the median follow-up was 21 years and 91% of the whole cohort had died. Key endpoints assessed were overall, cause-specific and relative survival. Comparisons were made between the first 15 years of follow-up and beyond 15 years.

It was found, on repeat biopsy, that 17% of tumours had dedifferentiated. Over the observation period 40% of patients had progressive disease of whom 17% had developed metastases. Of the whole cohort 16% died of prostate cancer rising to 22% in those who were under 70 years of age at the time of diagnosis. Survival was significantly poorer for those with poorly differentiated tumours. Cause-

specific survival decreased and mortality from prostate cancer increased after 15 years from diagnosis.

OPINION

The debate regarding the optimal management of patients with localised prostate cancer continues, with no consensus as to which patients need to be treated, let alone how to treat them.

There is no doubt that the majority of men will develop this disease if they live long enough. There is also no doubt that in some cases it will be 'clinically insignificant' with many patients dying 'with it rather than from it'. There is also, however, no doubt that this disease can be rapidly fatal and can be associated with very significant morbidity which will adversely affect a patient's quality of life even if it does not prove to be fatal.

Any information which will help clinician and patient to decide if immediate local treatment with its attendant morbidity is necessary, as opposed to deferred treatment, is to be welcomed. As the authors say 'the challenge is to maximise the possibilities for survival without extensive overtreatment'.

This is the latest of a series of papers following a cohort of patients managed by a deferred treatment policy remarkable for its size, its length of follow-up (essential for this disease), and its major endpoint – death. Whether or not the cause of death was prostate cancer was available in a remarkable 91% of the study group.

These data could probably be used equally successfully to support or refute the policy of deferred treatment and will almost certainly be interpreted differently by those who favour active intervention and those who do not. These data will not give us the answer to the question: Which patients should we treat? They are, however, extremely helpful in informing the discussion with patients as to the appropriateness of intervention at the time of diagnosis.

The effect of poor differentiation on prognosis is confirmed, and in most cases treatment should be offered to these patients. Also clearly shown is the inevitable dedifferentiation with time, and the inexorable progression of the disease apparently accelerating after 15 years.

The gamble is, will the cancer get you before something else does? For patients with well-differentiated tumours these data support the rule of thumb used for many years by clinicians, that is, will the patient survive ten years? If not, the deferred treatment option should be considered. You could argue that this series supports extending this timescale to 15 years.

Crucially missing are morbidity data. Even if intervention does not increase survival the avoidance of so-called 'catastrophic events' such as spinal cord compression is a useful endpoint in itself. Although for most clinicians the 'no immediate treatment' option is becoming more difficult to justify and this paper does not change that, these data do support the continued careful assessment of each individual patient and the option of no immediate treatment should still be up for discussion.

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This paper was coincidentally reviewed in Surgeons' News *from the Royal College of Surgeons of Edinburgh (Turner K and McNeill A. Prostate cancer: the waiting game.* Surgeons' News *October 2004; **3(4):**16). The 'second opinion' has been extracted and is reproduced below with the kind permission of* Surgeons' News *and K Turner and A McNeill.*

> Detailed 15-year follow up on this cohort of patients has been previously published. The data quality is high. No patients were lost to follow-up and the Swedish Death Register provides accurate information on the cause of death. Analysis of data from the last six years of this study (follow-up from 15–21 years) shows a surprising shift in the behaviour of prostate cancer with acceleration in progression and mortality beginning at around 16 years. Interpretation should be cautious. First, the advent of PSA testing and MRI/CT scanning in recent years may have facilitated recognition of progression. Second, the results are based on men with a mean age of >70 years and may not be directly applicable to current (younger) cohorts. Despite this, the study highlights that five-year follow-up may be needed before current management controversies can be resolved. Whilst we await firm evidence, aggressive treatment should be offered to young men with prostate cancer.

Clinical opinion: improving the preparedness of newly qualified doctors for the role of the pre-registration house officer

TITLE: The effect of an extended hospital induction on the perceived confidence and assessed clinical skills of newly qualified pre-registration house officers.
KEYWORDS: Clinical skills, induction programme, pre-registration house officer.
AUTHORS: Evans DE, Wood DF, Roberts CM.
JOURNAL: *Med Educ* 2004; **38:**998–1001.

SUMMARY
This short report explores the concerns that have been raised about the preparedness of new medical graduates for the role of pre-registration house officer (PRHO). The authors examined the self-assessment of preparedness, the objective assessment of core clinical skills, and the effect of an extended clinical induction programme in a cohort of 23 (26 in total, of whom two declined and one was unable to complete the follow-up due to pressure of work) new PRHOs in a district general hospital. The PRHOs completed a questionnaire and underwent an objective structured clinical examination (OSCE) of four core clinical skills prior to, immediately after and one month after a five-day ward-based induction.

Pre-induction results showed that PRHOs have low perceptions of their own abilities in all clinical scenarios and skills. In most cases this improved after induction, although in two areas their confidence actually deteriorated. Only one PRHO passed all four core clinical skill stations at the pre-induction OSCE. Seven failed on one or more skills at the end of the induction OSCE, although all were deemed competent at the one-month assessment.

The authors conclude that PRHOs do not feel prepared for the role they are about to assume and objective assessment of core clinical skills confirms that they are not prepared. An extended induction may go part, but not all, of the way to correct deficiencies.

OPINION
In some respects it is not surprising that newly qualified doctors have low levels of confidence in their own ability to perform the duties of a PRHO. Who can forget the first day as a doctor, the first night on call, the first arrest? The PRHO year is a life-changing experience, and as such new doctors are right to be apprehensive. It is interesting that the two areas where confidence deteriorated were in prescribing and death certification – two activities from which medical students are excluded by legislation – and therefore 'unknown territory' for them.

More surprising, and concerning, is their poor performance in core clinical skills. The assessed core clinical skills were; measuring BP, cannulation, venepuncture and catheterisation. Certainly core skills for any doctor, one would think! Why then do 96% fail one or more skills at pre-induction assessment? Seventy per cent cannot measure BP, 91% cannot cannulate, 22% cannot perform a venepuncture and 26% cannot catheterise. Disturbingly, despite undergoing a five-day induction, 26% still could not measure BP adequately and 9% still could not perform venepuncture properly.

Clearly the numbers are small and the findings must be viewed with caution. However, this cohort of PRHOs were all graduates of the same, unidentified but presumably London, medical school and one is left wondering why one in four still cannot perform elementary skills after five years of medical school and almost one in ten cannot perform elementary skills after a five-day intensive induction.

This paper raises important questions about how we prepare medical students for future practice but one wonders whether it might also raise questions about how we select them in the first place.

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Clinical opinion: treating chronic hepatitis C in patients co-infected with HIV

TITLE: Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients.

AUTHORS: Torriani FJ, Rodriguez-Torres M, Rockstroh JK *et al.* for the APRICOT Study Group.

KEYWORDS: Co-infection, hepatitis C virus, human immunodeficiency virus (HIV), preferred treatment.

JOURNAL: *N Engl J Med* 2004; **351(5):**438–50.

SUMMARY

The APRICOT study was a large international randomised controlled trial which recruited 868 patients co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) and assigned them randomly to receive either pegylated interferon (PEG) and ribavirin, PEG and placebo or standard interferon-α (IFN-α) and ribavirin. These patients had no previous HCV treatment (i.e. were treatment naïve) and had stable HIV disease, with or without highly active antiretroviral therapy (HAART). Patients were treated for 48 weeks, irrespective of genotype, and followed-up for a further 24 weeks.

Significantly better sustained viral response (SVR) rates were seen in patients treated with PEG and ribavirin (40%) compared with PEG and placebo (20%) or IFN-α and ribavirin (12%). Response to treatment was genotype dependent, with 62% of patients with genotypes 2 and 3 showing an SVR to PEG and ribavirin compared with 29% of genotype 1 patients. In genotype 1 only, lower pre-treatment HCV RNA levels were associated with improved response rates. Patients who had at least a 2 log10 drop in HCV RNA by week 12 were more likely to have an SVR at 24 weeks' follow-up post-treatment than those that had a poor virological response at week 12. HIV-related parameters such as CD4+ cell count and use or non-use of HAART were not independent factors associated with an SVR to HCV therapy. All patients included in the study had relatively well-controlled HIV with CD4+ counts greater than 200/ml^3 or greater than 100/ml^3 with HIV-1 RNA less than 5,000 copies/ml.

Approximately one-third of patients withdrew from the study before its completion. There were no differences between the groups in reporting of adverse events but patients treated with PEG (either with ribavirin or placebo) were more likely to require dose modification due to neutropaenia or thrombocytopenia. Those taking ribavirin were more likely to require dose adjustment for anaemia. Use of haemopoeitic growth factors by each group reflected this data. Less than 5% of patients in all arms of the trial required to be withdrawn completely from treatment due to laboratory abnormalities, haematological or biochemical. There was no difference in withdrawal rates between treatment groups.

OPINION

Currently PEG and ribavirin are recommended in combination for treatment of chronic HCV infection. Patients who are treated successfully have SVR to therapy, defined as HCV RNA lower than the limit of detection by polymerase chain reaction (PCR) methods 24 weeks after completion of treatment. An SVR is achieved in between 40% and 80% of patients. Response depends on HCV RNA levels before treatment and on virus genotype, with genotype 1 responding less well than 2 or 3.

HIV and HCV have common modes of infection and consequently, depending on the predominant route of transmission in a particular population, between 10% and 90% of HIV-infected individuals also have chronic HCV infection. HIV/HCV co-infected patients have significantly higher circulating HCV RNA levels than those with HCV infection alone and a number of studies have shown that compared with people who have HCV mono-infection, HCV induced liver disease is more severe in those with HIV/HCV co-infection, particularly where CD4+ counts are low, than in those with HCV infection alone.

Since 1996 HAART has led to a dramatic improvement in HIV-related morbidity and mortality. However this now means that a significant proportion of ill-health in the HIV-positive population is due to HCV-related liver disease. Treatment of HCV in co-infected patients has proved difficult in terms of haematological side-effects, hepatotoxicity and drug interaction with HAART regimes.

This study confirms that accepted data regarding the treatment of HCV mono-infection holds true for

the HIV/HCV co-infected population. Response is genotype dependent, although in contrast to those infected with only HCV genotypes 2 and 3 may require a full 48 weeks of treatment in co-infection. SVR is also more likely if pre-treatment HCV RNA levels are lower and the predictive value of early viral response can also be applied to this population.

SVR rates are still much lower in co-infected patients than in those with HCV alone, particularly in those with genotype 1 and high HCV RNA titres. However, response rates are significantly better with PEG compared with standard IFNα. Even PEG alone gave a reasonable SVR compared with standard combination therapy, providing a more favourable option to patients for whom ribavirin is not tolerated or is contraindicated.

SVR rates were significantly higher in this study than in two similar studies, one of which was reported in the same issue of the *New England Journal of Medicine*. Although both these trials confirmed the additional benefit of pegylated compared with standard interferon in addition to ribavirin, SVR rates were around 27% in the PEG group and 12% in the standard combination arm. The three trials were not designed to be directly comparable as one used a different form of PEG and the others a different treatment population. Absolute response rates should therefore be interpreted with care. Further studies of the treatment of HCV in this population are required before accurate SVR rates will be known.

This study clearly illustrates that HIV/HCV co-infected patients should now have their hepatitis C treated with combination PEG and ribavirin. It shows that PEG is an effective treatment for HCV in those co-infected with HIV. Safety data from the trial also illustrate that PEG and ribavirin can be safely used in this population if done so with care, appropriate dose modification and with the support of haemopoeitic factors where necessary. This study is important in its confirmation of PEG as an effective treatment for HCV infection in those co-infected with HIV. It also illustrates that PEG and ribavirin can be safely used in this population, if done so with care, appropriate dose modification and with the support of haemopoeitic factors where necessary.

DECLARATION OF INTERESTS
HM Younger and PC Hayes have both received funding and travel costs from Schering-Plough and Roche to attend conferences.

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