

Possible treatments for hepatitis C — what's currently in the pipeline?

Most of the 200,000 people in the UK who are chronically infected with hepatitis C are not aware of the fact and the incidence of resulting liver disease is predicted to rise. Jenny Bryan looks at recent developments in the search for hepatitis C treatments

Promising results with a new generation of treatments for hepatitis C will be welcome news for those analysing the gloomy statistics and predictions about the infection, published in the Health Protection Agency's first annual report on hepatitis C last month.¹ Over 200,000 people in the UK are thought to be chronically infected, most without knowing it, and the number of people with severe hepatitis C-related liver disease in England and Wales is predicted to rise from around 4,500 in 2005 to 7,000 in 2010.

Current treatment of hepatitis C (HCV) — for the minority of people who have been diagnosed — is based on a combination of pegylated interferon alpha and ribavirin.² Overall, this leaves about 55 per cent of patients free of virus at six months (45 per cent of those with the hardest to treat, genotype 1 virus, and up to 80 per cent of those with the more responsive genotypes 2 or 3).¹

But success rates are lower in groups such as those of African-Caribbean origin and in people who are overweight, and only about one in 10 of those who fail to clear the virus with a first course of treatment will do so with retreatment.

Novel treatments for HCV are currently focusing on three distinct aspects of the infection — the key protease and polymerase enzymes needed for viral replication, the host factors which the virus hijacks to aid replication, and the immune modulators which trigger the body's own defences against infection.

The HCV genome encodes a large precursor polyprotein which is cleaved by viral and host proteases to form at least 10 functional proteins — core, envelope E1, E2 and p7, and non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

At a recent American Association for the Study of Liver Diseases (AASLD) meeting in San Francisco, California, Stefan Zeuzem, from Saarland University, Homburg, Germany, explained that the NS3 protease is proving a popular target for some of the new anti-HCV therapies.

"NS3 protease is a highly attractive target for treatment because it has a pivotal function in the cleavage of non-structural proteins that are important for replication of the virus," he said.

Phase 1, short-term, dose-ranging studies of the protease inhibitors, SCH 505034, developed by Schering Plough, and VX-950, from US-based biotechnology firm, Vertex Pharmaceuticals, have shown promising reductions in viral load in patients with refrac-

tory genotype 1 HCV, and the drugs appear well tolerated. A large phase II study of SCH 505034 in combination with pegylated interferon alpha-2b, with or without ribavirin, is under way, and studies of VX-950 are also continuing.

Already successfully through its first phase II studies is Idenix Pharmaceutical's valopicitabine (NM283), an inhibitor of the NS5B polymerase enzyme which is also essential for HCV replication.

In HCV genotype 1 non-responders to previous treatment, significantly more patients treated with a combination of pegylated interferon and valopicitabine for 12 weeks achieved an early viral response (greater than 2-log₁₀ reduction in viral load) than those treated with pegylated interferon and ribavirin. Phase III clinical trials are planned for 2006.

"The patients in the trial had failed other treatment, so it is very exciting that valopicitabine and pegylated interferon showed an advantage over standard retreatment," said Christopher O'Brien, from the University of Miami, Florida.

Drugs that target host factors required in the HCV lifecycle could be used as complementary treatment to viral protease and polymerase inhibitors. Cyclophilins are cellular factors which facilitate protein conformation and at least one of these, cyclophilin B, is known to interact with HCV polymerase NS5B to stimulate its RNA binding activity, and hence to aid HCV replication.³

Both the immunosuppressant, cyclosporin A, and its non-immunosuppressant analogue, NIM811, under development at Novartis, have been shown to bind to cyclophilins, with resulting reductions in HCV RNA levels.

Another host target that could be useful for inhibiting HCV replication appears to be sphingolipid biosynthesis. The NS5B protein



Hepatitis C: gloomy statistics and predictions

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has a binding site for host cell sphingolipids, and the interaction is thought to be necessary for HCV replication.

At the AASLD meeting, the Japanese company Chugai Pharmaceuticals reported that its inhibitor of sphingolipid synthesis, NA255, derived from a secondary fungal metabolite, suppresses HCV replication in a dose-dependent way. Reassuringly, the Chugai researchers found that NA255 appears to have no effect on host cell viability or cell cycle progression.

Stimulating the immune system to mount a response sufficient to achieve sustained HCV clearance is another attractive option, and the family of Toll-like-receptors (TLR) that are expressed on immune cells and initiate inflammatory responses to microbial invasion are being targeted by HCV researchers.

TLR9 is expressed on plasmacytoid dendritic cells (pDC), also known as natural interferon-producing cells. Stimulation of

TLR9 leads to secretion of interferons alpha and beta, and activation of the cellular components of innate and adaptive immune responses needed for HCV control, notably T cells, natural killer (NK) cells, pDC and B cells.

John McHutchison, from Duke University, Durham, reported promising cytokine and cellular effects of the TLR9 agonist — actilon (CPG10101) — being developed by US firm, Coley Pharmaceuticals. In a study of 48 healthy volunteers and 60 HCV patients, actilon treatment was associated with activation of peripheral T cells, NK cells and monocytes in a dose-dependent manner, within 24 hours of the first dose. Cellular activation was spontaneously reversible within three to five days, suggesting that treatment does not induce uncontrolled immune or inflammatory responses. Larger studies of Actilon, over longer periods of time, and in combination with pegylated interferon and ribavirin are under way.

Assuming that some of these novel approaches to HCV treatment successfully complete their clinical trial programmes, the

question will be how they will fit with current therapies.

HCV researchers at AASLD predicted that protease or polymerase inhibitors, or both, will be combined with pegylated interferon, rather than replace it, as will immune modulators. However, it may be possible to disperse with ribavirin, whose side effects can limit dosing and duration of treatment. The big hope is that, given the relative lack of potency of the hepatitis C virus, HCV patients will need to take their protease inhibitors for weeks or months instead of the lifelong treatment required for HIV.

In the even longer term, a vaccine against HCV remains a possibility. First clinical data on a novel HCV vaccine which targets the E1E2 envelope proteins of the virus were reported by Adrian DiBisceglie and colleagues at the St Louis University School of Medicine, Missouri. Significant antibody and lymphocyte proliferation responses were detectable as early as two weeks after the third of four vaccinations administered over 48 weeks. The vaccine was relatively well toler-

ated in the 60 adult subjects who were immunised, with injection site pain, myalgia and headache the most commonly reported adverse events. Other HCV vaccines are in research but not, as yet, in human trials.

For the next few years at least, the growing number of people diagnosed with HCV in the UK will continue to rely on pegylated interferon/ribavirin regimens, with doses and duration of treatment increasingly tailored to the genotype of the virus with which they are infected, their ethnic group and their comorbidities.

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MURs: how the picture is developing

Medicines use review was introduced as an element of the new community pharmacy framework for England and Wales in April 2005. In this article, **Angela Alexander** outlines progress so far

Medicines use review (MUR) was a first in many ways. It was the first nationally commissioned service (other than dispensing), the first service to require accreditation of both pharmacists and pharmacy premises, and the first service to have a specified set of competencies. MUR also presents the first opportunity within the new contract for community pharmacists in England and Wales to demonstrate the added value that they give to the communities they serve. Some might even say that the commissioning of future enhanced services depends on the demonstrated success of this advanced service.

In addition to providing an opportunity to demonstrate the added value that the input of pharmacists will bring to health care, however, MUR also presents some recognised threats. Panel 1 (p45) presents the responses to SWOT (strengths, weaknesses, opportunities, and threats) analyses undertaken by five groups of pharmacists who attended MUR training workshops run by the University of Reading.

Accreditation

MUR requires accredited premises and pharmacists. The review must take place in a confidential environment and consultation areas must meet the following requirements:

- The patient and pharmacist can sit down together
- The patient and pharmacist can talk at normal speaking volumes without being overheard by pharmacy staff or customers
- The area is clearly signed as a private consultation area

Meeting these requirements has been a challenge for many pharmacies. Some have undergone radical refits or have incorporated minor changes to reinforce the sound proofing of existing quiet areas. Others have installed units that have been likened to Dr Who's Tardis.

Accreditation of pharmacists has been achieved through equally diverse methods. The Department of Health required accreditation to be conducted by higher education institutes, which were challenged to assess the competence of the pharmacist against a defined competency framework.¹ Ideally, competence would be assessed by observing practice or by using an objective structured clinical examination. However, with a potential cohort in excess of 12,000 such assessment is not possible.

The Medway School of Pharmacy was first off the mark. It required pharmacists to produce responses to video-taped MUR interviews. The University of Reading followed with a portfolio assessment requiring answers to a case study, the completion of two MURs and a reflective report. Similar portfolio assessments were introduced by the Welsh

School of Pharmacy. The University of Manchester, in collaboration with the Centre for Pharmacy Postgraduate Education (CPPE), has produced an online assessment which combines multiple choice questions with case study responses and completion of an MUR document. Other higher education institutes providing postgraduate courses have incorporated MUR assessment into their modules. Concerns over the methods used to assess competency have, however, been expressed.² The lack of direct assessment of consultation and decision-making skills was thought to have implications for the effectiveness of the service to patients and the NHS.

Primary care organisations

The service specification for MUR³ states that primary care organisations (PCOs), working with their community pharmacies, may identify specific patient groups who would be appropriate for targeting, based on the needs of the local health economy. As might be expected this leads to extensive variation; some suggestions for target groups being more imaginative than others. Panel 2 (p46) lists some of the target patients that PCOs have identified.

Concern has been expressed over duplication of MURs and the medication reviews conducted in general practices as part of the new general medical services (GMS) contract. This could lead to patient confusion or inefficient use of health care professionals'

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time, or both. Avoiding unnecessary duplication requires joint working between pharmacies and GP practices. Some PCOs have recognised that MURs can contribute to the Quality and Outcomes Framework (QOF) of the GMS contract. GPs in such PCOs may be more likely to welcome pharmacist-performed MURs.

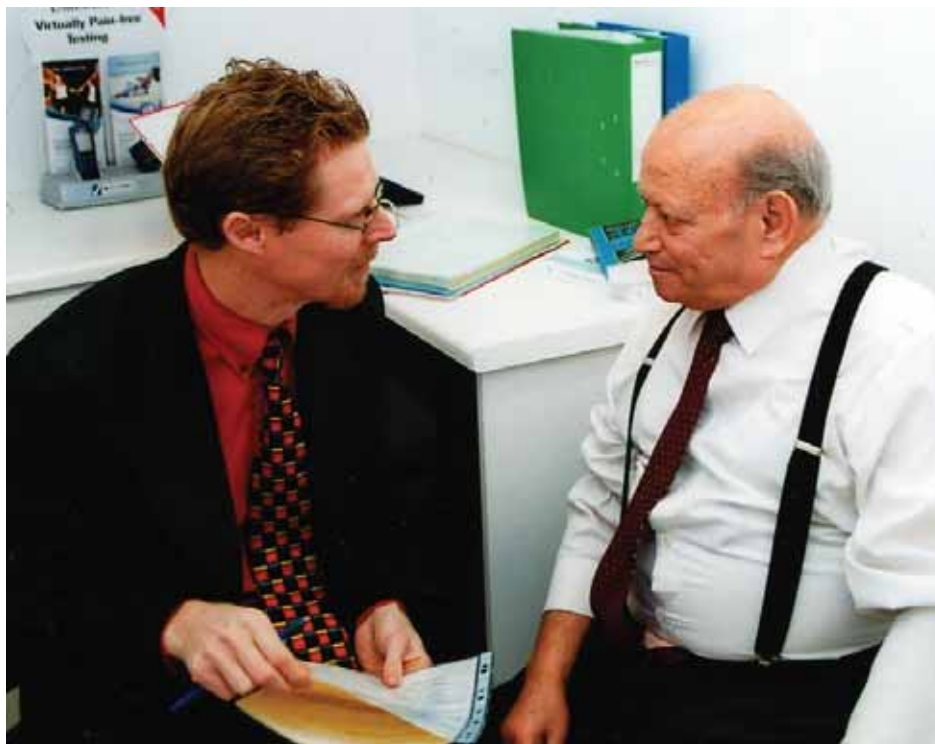
Medication review is included in the QOF for some groups of patients (eg, patients aged 16 years or over and taking medicines for epilepsy, patients with severe long-term mental health problems and patients being prescribed four or more repeat medicines). Although it is accepted that MUR is not the same as a medication review, as defined in the national guidance document "Room for review",⁴ it is recognised that MUR does contribute a considerable element towards medication review. Making links between the contracts for pharmacists and general practice should help to forge links between the two professions.

The service specification for MUR states that pharmacists may accept referrals from other health care professionals. Some PCOs have identified links with the new primary care or community matrons' role and have suggested that they refer patients identified as having problems managing their medicines, and those who are frequently admitted to hospital, to a pharmacist for advice.⁵ Referral forms have been designed by some PCOs for such use.

Registration and monitoring

In England, primary care trusts (PCTs) require those pharmacists who wish to perform MURs to register by completing a declaration stating that they are already complying with the essential services, and that their premises meet requirements. In addition, pharmacists must submit their higher education institute certificates from MUR accreditation. This raises the question of how pharmacists who provide locum services across a large number of PCTs can be recognised as being able to provide MURs. In Wales there are separate forms for a contractor to self-certify to the local health board (LHB) that his or her premises meet the required standards of the new pharmacy contract and for pharmacists to inform the LHB of their suitability to provide MURs. A pharmacist will only have to register at one LHB to be eligible to practise in any LHB across Wales, subject to the premises being suitable.

In England, the NHS Primary Care Contracting team has developed guidelines for monitoring the MUR service as an element of the Community Pharmacy Assurance Framework.⁶ Consultation areas will be tested by one observer holding a conversation with the pharmacist in the consultation area, while a second observer remains in the public or staff areas. If the outside observer cannot tell what has been said, then the area is considered to comply with the criteria.



The patient and pharmacist should be able to sit down together

The guidelines suggest that MUR records should also be reviewed. There is a requirement that both the PCO and the pharmacists follow data protection and confidentiality procedures. Primary Care Contracting suggests that when pharmacists are required to produce manual records it should be a maximum of 20 records. The proposed verification of the MUR record seems a rather cumbersome process. The person carrying out the monitoring will ask the pharmacist to read out the record of medicines prescribed and the dates of MURs randomly selected by the monitor, who will

also write down these medicines. The pharmacist should then be asked to produce anonymised patient medication records for those patients. Comparison of the medicines prescribed will allow verification that the correct patient record has been produced, without the patient's identifiers being included.

This process may become more streamlined with the development of electronic recording on MURs, enabling anonymised cross referencing. Pharmacy systems suppliers have already developed functions to support the electronic recording of MURs, including

Panel 1: SWOT analysis of MUR

Strengths

- Builds relationship with patients
- Affirms professional role
- Builds relationship with primary care organisations (PCOs) and GPs
- Provides job satisfaction
- Provides a new income stream
- Contributes to continuing professional development
- Increases confidence

Opportunities

- Increase in customer loyalty
- Development of support staff to free pharmacists' time
- Build relationships with PCOs and GPs
- Potential to link to general medical services contract
- Demonstrates what pharmacists can do
- Chances to improve patient care (eg, improved self-care and concordance)
- Retention of pharmacists

Weaknesses

- Requires time and resources
- Paper-based service at present (paperless systems are less cumbersome)
- No access to patient records at present
- Lack of GP and patient awareness
- Restriction on numbers of MURs that can be done
- May be unable to meet patient expectations
- Housebound patients may not be able to access service

Threats

- Could damage relationship with GPs
- Patients could be confused if conflicting advice is given
- Could lose patients if service is not up to standards
- Standards may vary among pharmacies and it is possible for MURs to be performed poorly
- Possible increase in NHS spend

the generation of printed copies of MUR form.

Support for MUR

The potential for the pharmaceutical industry to support community pharmacists who provide MURs has not gone unnoticed.⁷ Improved compliance is of interest because it increases medicines use and, therefore, sales. Pharmacists may also be making recommendations for medication review with the potential for a change in prescribing.

Many wholesalers see MUR as a service for which they can provide support. Numark has launched a toolkit to help its members carry out MURs.⁸ It features details of accreditation, advice on how to select and invite patients for review, a template standard operating procedure and marketing material in the form of leaflets and a poster.

Mawdsleys has produced a guide to MUR, which lists some introductory "dos and don'ts".⁹ In the Mawdsleys guide it is suggested that, for the first year, after taking into account the costs of training, additional communication with PCOs and GPs, and premises alterations, MUR would be conducted at a net loss to the contractor. However, there has been a recent increase in the number of MURs per year that can be funded, from 200 to 250.¹⁰ Under the current funding arrangements a pharmacy can be paid up to £5,750 for carrying out the maximum number of MURs.

The guide also suggests that an off-site option, such as surgery-based MUR, would be more profitable. However that would require approval by the PCO and the requirement for the pharmacy premises to be accredited still remains.

In support of the training required by employee pharmacists to become accredited to provide MUR, at least one of the multiples is providing a financial reward. A recent recruitment advertisement in *The Pharmaceutical Journal* stated that pharmacists who had achieved accreditation were eligible for a one-off payment of £750 three months after delivering MURs.

Changes to the roles and responsibilities of the current workforce may be needed as a result of offering an MUR service. If a pharmacist is engaged in private conversation with a patient, other mechanisms need to be put into place to ensure the rest of the pharmacy work continues. This may involve employing a second pharmacist or the skills of a checking technician. The recent announcement of the Health Bill, which enables changes to the Medicines Act to allow registered and suitably trained staff to supervise dispensing and medicine sales without direct supervision by a pharmacist,¹¹ will also enable different patterns of working. The Council of the Royal Pharmaceutical Society recently agreed new guidance on supervision during consultations.¹²

Patients may have to get accustomed to either waiting to see a pharmacist or making an appointment to return at a later time. It will

Panel 2: Examples of PCO recommendations for MURs

Patients with specific conditions, for example:

- Diabetes
- Stroke
- Heart failure
- Coronary heart disease
- Epilepsy
- Depression
- Chronic obstructive pulmonary disease
- Asthma
- Mental health (with severe or enduring problems)

Patients receiving specific types of drug, for example:

- Proton pump inhibitors
- Non-steroidal anti-inflammatory drugs
- Benzodiazepines or "z-drugs" (zopiclone, zolpidem, zalepon)
- Vitamins
- Enteral formula feeds

Patients with specific characteristics, for example:

- Those aged over 75 years and taking more than four medicines
- Those who are frail and elderly
- Frequent fallers
- Those who are frequently admitted to hospital
- Those recently discharged from hospital
- Those receiving medicines from more than one prescriber
- Those with significant changes to medication in the past three months
- Those in whom non-compliance is suspected
- Those with asthma who are under 18 years old

be interesting to see how this will affect the current dynamics of the pharmacy service.

Patient response and outcomes

Time will tell how patients react to MURs. Commitment to the service will be required if pharmacists are to achieve good attendance rates for planned appointments. Anecdotally some high non-attendance rates have been reported.¹³ Information for patients, explaining the service, is vital to improve understanding and attendance. Patient leaflets and posters have been produced by some of the multiples and by Numark, to support independent pharmacists. Some PCOs have also produced patient information leaflets.

Support from patient groups is also important to engender patient acceptance of MURs. Diabetes UK supports the new community pharmacy contractual framework and has said that for people with diabetes, specific benefits could include improved access to medicines management information and advice¹⁴ — presumably a reference to the value of MUR.

The results of the HOMER study,¹⁵ a randomised controlled trial of pharmacist-conducted medication reviews on patients

recently discharged from hospital presented a cautionary note for predicting the value of MUR. The authors reported that the study showed that home-based medication reviews conducted by a pharmacist were associated with increased hospital admission rates in older people, and suggested that these patients were somehow disadvantaged by pharmacist home visits. Another interpretation of this counter-intuitive conclusion is that the trial showed that pharmacists unmasked the clinical needs of patients which were then not met, increasing hospital admission.¹⁶

It has been suggested that by following criteria for effective medication review, MURs will bring benefits to patients and the NHS.¹⁷ Research into the value of MURs is eagerly awaited.

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