

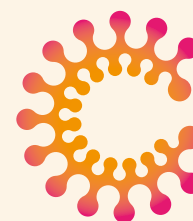
Treatment Guidance for Patients with Hepatitis C in Greater Manchester

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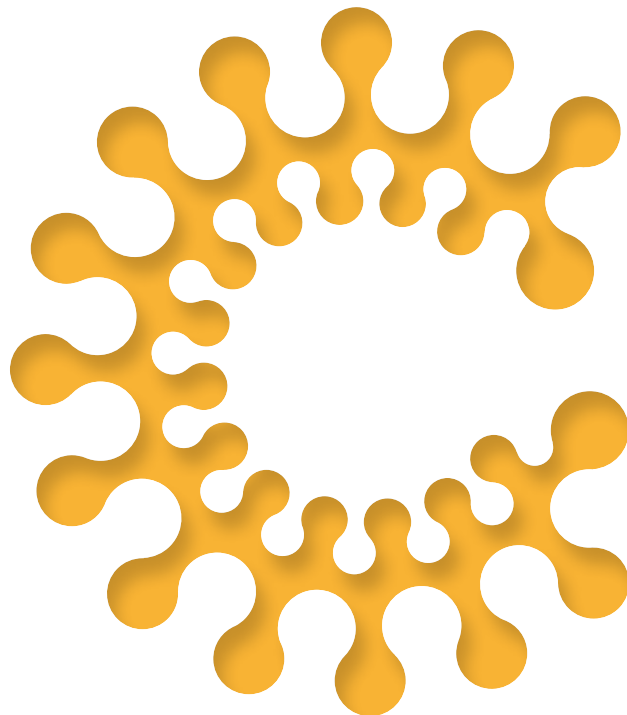


Hepatitis C

Greater Manchester Hepatitis C Strategy

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Definitions of responses to treatment

Sustained viral response (SVR): Undetectable levels of hepatitis C RNA* (PCR) on blood testing 6 months after completion of antiviral therapy. This is the ultimate aim of therapy as it is associated with long term remission from active infection and marked reduction in the frequency of complications of liver failure and hepatocellular carcinoma.

End of treatment response (ETR): Undetectable levels of hepatitis C RNA on blood testing at the end of planned treatment.

Primary non-responder: A patient who fails to achieve an end of treatment response, or in whom treatment is stopped early because to early blood tests show failure of viral suppression below pre-determined values that predict failure of response.

Responder-relapser: A patient who achieves an end-of treatment response but has recurrence of detectable virus six-months after treatment cessation.

Early viral response (EVR): A 2-log or greater reduction in viral levels 12 weeks after starting treatment. EVRs may be classed as complete (negative PCR at week 12 – cEVR) or incomplete (positive PCR but viral load shows greater than 2 log reduction from pre-treatment levels – iEVR).

Rapid viral response (RVR): Undetectable levels of hepatitis C RNA 4 weeks after starting treatment.

* For the purpose of this guidance undetectable RNA will be considered as <50 IU /ml as the PCR test is unreliable below that level.

Nice guidance: This was published in August 2006, updating the guidance from January 2004. Their review date was November 2007 but a review date October 2010 has now being proposed.

That guidance has now being complemented by a significant body of research about individualising treatment duration and side-effect management to achieve maximum response. This guidance includes this evidence to complement and update existing NICE guidance.

Notes 1. Ribavirin dosing

Two preparations of non-generic ribavirin are currently licensed for treatment of hepatitis C (Copegus and Rebetol). Each of these is licensed only with one form of Pegylated interferon 2 (IFN-2a and IFN-2b respectively). The licensed dosages of the two ribavirin preparations differ, although there is no evidence of differences in the pharmacokinetics of these products.

Higher doses of ribavirin relative to patient weight have been associated with improved response rates.^{1,2} In a recent large randomised controlled trial weight based dosing of ribavirin was shown to be associated with increased SVR compared to non-weight based dosing (44% vs 40%).² Given the absence of clinical evidence supporting non-weight based dosing all the protocols below use the following dose of both ribavirin products. For patients at certain weights this will lead to slight variation (200mg daily) from the licensed dose for a particular preparation

Patient weight	Daily Ribavirin dose
<65kg	800mg
65-85kg	1000mg
85-105kg	1200mg
>105kg*	1400mg

Interferon dosing and response rates

Unless explicitly stated in the text, response rates for interferon 2a & 2b are not directly comparable as they are drawn from separate trials on differing populations. In most cases there is little head to head evidence from high quality RCTs. Where there is an evidence based reason to consider one preparation over another this is stated in the text.

Pegylated IFN2A is licensed at a single dose of 180mg daily. Pegylated IFN2B is licensed at 1.5mg / kg body weight (maximum dose 150mg daily.). In heavier patients (>85kg), it may be appropriate to consider the choice between weight based and non-weight based interferon.

Treatment protocols

Genotype 1 or 4 hepatitis C without HIV co-infection

Registration trials of combination therapy for hepatitis C with Pegylated interferon and Ribavirin indicated a SVR of between 46% (IFN 2A)³ and 42% (IFN 2B)¹ with 48 weeks of therapy. This rate was higher than with 24 weeks of therapy⁴. In addition patients failing to achieve a 2-log or greater fall in viral load at treatment week 12 (i.e. EVR) were very unlikely to achieve a SVR (3%).³ Hence current NICE guidance suggests patients with genotype 1 or 4 hepatitis C should receive a standard 48 week course of combination therapy with Pegylated IFN and Ribavirin, with PCR measurements at 12 weeks and treatment cessation for patients failing to achieve EVR.

More recent work has supported the use of regimes tailored to patients' pre-treatment probability of success and early response to therapy. These may give improved overall response rates, & allow earlier stopping of therapy. RVR has been recently been identified as a very strong predictor of SVR and is even more powerful than genotype in this regard.⁵ Patients who achieve RVR in the absence of other poor prognostic factors (high fibrosis/cirrhosis, old age, co-infection, heavy weight) may be considered for shorter duration of treatment at the discretion of their consultants & after informed discussions with the patient.

Patients with a low viral load (600,000 IU) prior to treatment and pre-cirrhotic fibrosis achieving complete RVR and EVR have similar SVRs with 24 or 48 weeks of therapy (89% vs.85% with IFN 2B)⁶ and treatment may thus be halted at 24 weeks in these patients without adverse effect, reducing side effect and financial costs.

Patients without both of these pre-treatment conditions or who do not achieve RVR, but do achieve complete EVR should continue 48 weeks of treatment as per current NICE guidelines.

Patients who do achieve only an incomplete EVR (slow responders) should have repeat PCR measurements at 24 weeks.

If they have detectable PCR at any level at this point treatment should be stopped at this point as they are unlikely to achieve SVR.⁷

However if the PCR at 24 weeks is negative, treatment should be extended to 72 weeks since this is associated with improved SVR (from 32% vs. 45% IFN2A⁸ 18% vs. 38% IFN2B⁹).

This regime is summarised in the flow chart below. We recommend that treatment regimes are modified to this "tailored" protocol. This tailored protocol has been audited at St Mary's Hospital in London, and in this real world clinic it was found that the mean duration of therapy was reduced whilst the overall SVR rate was increased (i.e. more successful treatments were obtained with less medication use). (A Brown personal communication). This is backup by a recent review at North Manchester where all patients were assessed for treatment reduction or extensions. Every 3 patients who were able to reduced the course, one who needed extension was found out .

Recently a large multicentre study has directly compared response rates in patients infected with genotype 1 hepatitis C using Pegylated IFN 2A and 2B (ribavirin doses differed slightly in the arms of the trial).¹⁰ The study found similar SVR rates with both IFN formulations and also with reduced dose IFN2B (1.0mcg/kg compared to 1.5mcg/kg). IFN2A was associated with a higher end of treatment response but also a higher relapse rate. Currently unpublished data suggests that IFN2B was associated with improved predictability of SVR from EVR. At present this data is insufficient to mandate that all patients are treated with only one form of Pegylated IFN although it may guide treatment decisions in individual patients and may require updating when this trial is published in full. .

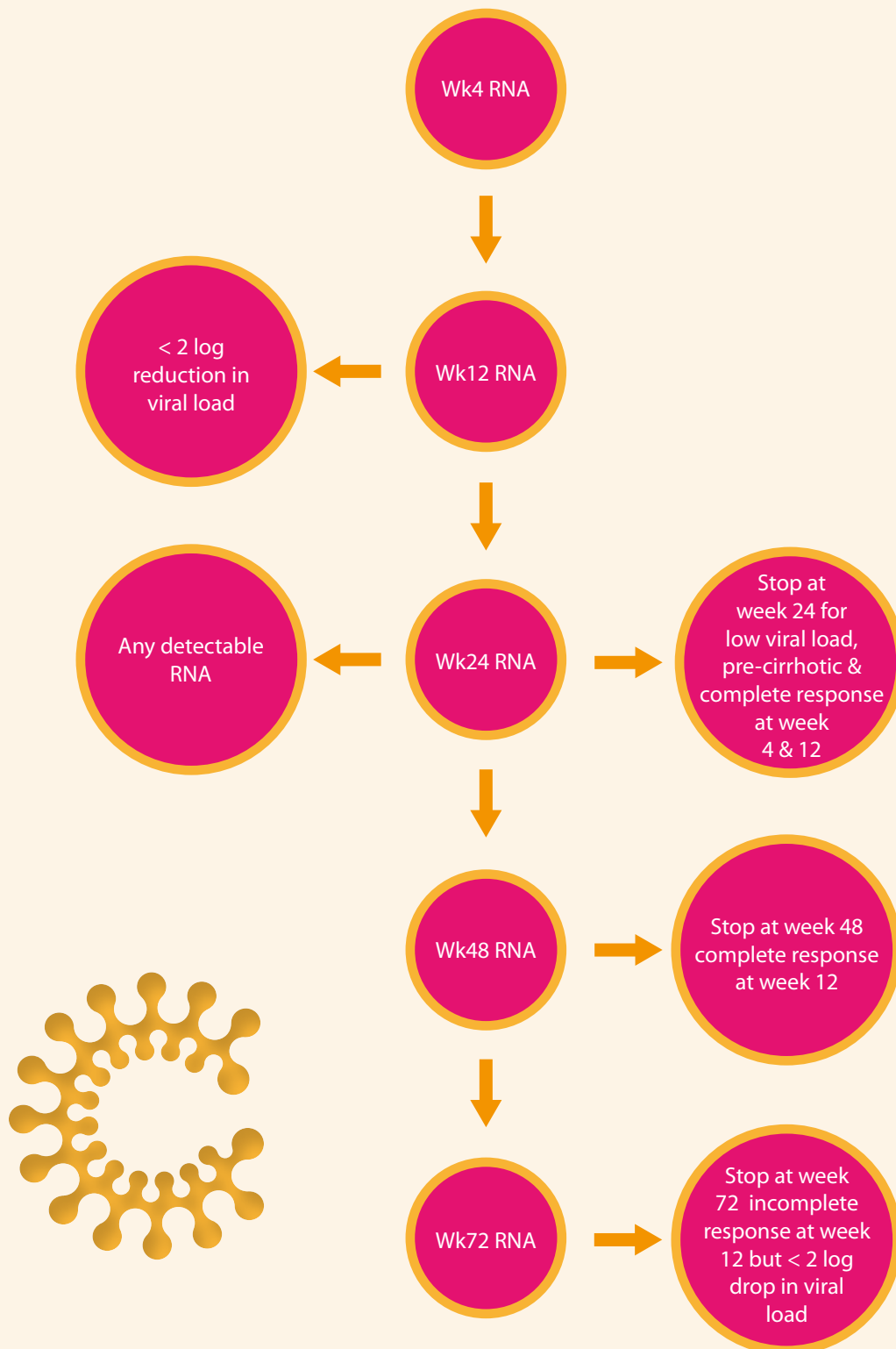
Summary: Genotype 1 or 4 hepatitis C without HIV con-infection

Patients with genotype 1 or 4 Hepatitis C should receive 24 – 72 weeks of weight based ribavirin and Pegylated IFN (2A or 2B). Treatment should be stopped for non-efficacy for patients not achieving EVR or with positive PCR at week 24. Standard treatment length 48 weeks. Consider stopping treatment early (at week 24) if there is a RVR and cEVR and patient has low viral load and is pre-cirrhotic. Consider extending treatment to 72 weeks for patients achieving only incomplete EVR provided PCR negative at week 24.

Treatment
cessation for
treatment
failure

G1
hepatitis C

Treatment
cessation for
treatment
failure



Genotype 2 or 3 hepatitis C without HIV co-infection

Patients with hepatitis C genotype 2 or 3 have a high rate of SVR with 24 weeks Pegylated interferon and Ribavirin (76% IFN 2A¹¹, 76% IFN 2B¹²). This is not significantly improved by extending therapy to 48 weeks.⁴ NICE guidance recommends treatment for 24 weeks with combination Pegylated IFN and Ribavirin.

Previously patients with cirrhosis have received 48 weeks of treatment in some centres in order to minimise relapse rates based on theoretical data on treatment efficacy and a lack of sufficient data to guide treatment from individual registration trials. Data collated from multiple registration trials has now been published in the grey literature has shown no advantage for this prolongation of therapy¹³ and we recommend that treatment usually limited to 24 weeks, unless other poor prognostic factors are present (for example failure to achieve RVR, slow response (incomplete EVR), heavy weight) until further evidence is published (a large multicentre RCT to examine the optimal treatment for patients with cirrhotic genotype 2 or 3 hepatitis C is currently being planned).

The SVR for patients with good prognostic markers (age <40 years, viral load < 800,000 IU/ml early fibrosis, and a RVR) is similar for 12 and 24 weeks of treatment.¹² Patients in this category may be offered shortened treatment (16 weeks) after appropriate counselling at their first appointment following a 12 week blood test. (Many patients with genotype 2 or 3 HCV will not have had liver biopsy and proxy markers of fibrosis severity (such as platelet count) may need to be considered when assessing likely degree of fibrosis.)

Summary: Genotyp 2 or 3 hepatitis C without HIV con-infection

24 weeks of weight based ribavirin and Pegylated IFN (2A or 2B). Consider stopping treatment early (at week 16) if there is a RVR and complete EVR and patient is pre-cirrhotic had an initial viral load <800,000 IU.

Patients with established renal failure on dialysis

Hepatitis C infected patients on dialysis have a reduced survival. Ribavirin is contraindicated due to increased risk of anaemia, and IFN doses require adjustment. Retrospective and prospective studies have tended to show better tolerability and SVR rates with Pegylated IFN 2A than 2B (reviewed in Liu et al¹⁴) Two recent small RCTs have compared strategies for treating hepatitis C in patients on dialysis. Peck-Radosavljevic et al¹⁵ compared two doses of Pegylated IFN 2A (135 µg vs. 90µg weekly) both for prescribed for 48 weeks. Overall SVR rates were similar in both groups (39% vs. 35% all patients, 31% vs. 38% genotype 1). They also found that failure to achieve a complete EVR was associated with very low rates of SVR (4-8%). Liu et al¹⁴ compared 24 weeks of Pegylated IFN 2A to non-Pegylated IFN and found improved SVR rates in patients on Pegylated IFN (40% vs. 28%). Insufficient data exists to suggest whether treatment should be reduced to 24 weeks for patients with favourable genotypes (2 or 3).

In patients awaiting renal transplantation it may be appropriate to consider timing of the transplant in treatment decisions as it may be possible to use combination therapy post-transplant. However, immunosuppression needed for renal transplantation may also accelerate the course of the hepatitis C and decisions should be tailored to patients' individual requirements.

Summary: Patients with established renal failure on dialysis

Patients on dialysis needing treatment should receive 48 weeks of Pegylated IFN 2A monotherapy at reduced dosage (135µg weekly). Treatment should be stopped at week 16 if the patient does not achieve complete viral suppression at week 12.

Patients with coinfection with HIV

Patients with HIV and hepatitis C co-infection have an accelerated progression of liver fibrosis and should be considered early for treatment, following the British HIV association (BHIVA) guidelines.¹⁶ Treatment is less likely to be effective if the CD4 count is less than 350 cells/ml. Patients with CD4 counts below this should receive HAART to improve their immune response prior to interferon treatment, and ideally improve their CD4 count to above 350 cells/ml. Some agents used in HAART (zidovudine, didanosine and abacavir) interact with ribavirin. For these reasons all coinfecting patients should be cared for by physicians or multidisciplinary teams with experience in managing both HIV and hepatitis C

Although there are studies using both Pegylated IFN 2A and 2B interpretation of the studies using 2B is difficult due to the high drop out rate.¹⁶ In the largest RCT (the APRICOT study)¹⁷ 48 weeks of combined PEGylated IFN 2A (180mcg) and ribavirin therapy was associated with an SVR of 29% for genotype 1 and 62% for genotype 2/3. Treatment was rarely successful in patients not achieving an EVR.

There are some data to suggest that those patients with genotype 2 or 3 who obtain RVR have a good SVR with just 24 weeks of treatment.¹⁸ This may be considered in experienced centres in patients with otherwise good prognostic factors.

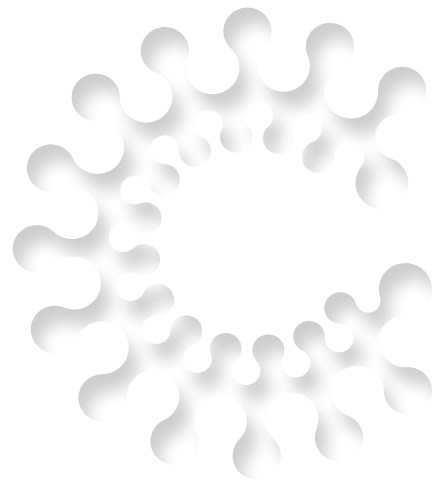
Summary: Patients with co-infection with HIV

Patients with HIV and hepatitis C should receive 48 weeks of weight based ribavirin and Pegylated IFN 2A (180mcg weekly). This may be reduced in genotype 2/3 infected patients with a RVR and good prognostic factors Treatment should be stopped at week 16 if the patient does not achieve at least a 2-log reduction in viral load at week 12. Treatment should be withheld in patients with a CD4 count <200 / ml until this is corrected with HAART. Treatment should be limited to experienced centres.

Patients with decompensated cirrhosis

Patients with cirrhosis associated with low platelet counts (<50), haemoglobin (<10g/l) or white cell counts (<0.75) or with moderate hepatic decompensation (Child – Pugh grade B) are at markedly increased risk of complications of therapy. However, these are also the patients at highest risk of serious complications from untreated hepatitis C and need of transplant. Such patients should all be cared for in a hepatology centre or in a multidisciplinary team closely linked to such a centre. 48 weeks of treatment with a low dose accelerating regime (LADR) has been recommended for these patients as this allows patients to gradually build up to the maximum dose of antiviral therapy tolerated.

These regimes should be used by physicians with experience of managing such difficult patients. We recommend the use of a LADR such as that used in King's college hospital which is well established & summarised overleaf.



LAD Regime (based on King College Hospital regime)

Initial dosage regime: Pegylated interferon 2a[PEGASYS] and ribavirin [COPEGUS]

Starting dose based on assessment of tolerability & previous history

Base visit: commence peg 45mcg sc weekly (if dose tolerated)

2 week review: increase to peg 90mcg sc weekly (if dose tolerated)

4 week review: add ribavirin 200mg bd daily (if dose tolerated)

6 week review: increase to 135mcg sc weekly and 400mg ribavirin (if dose tolerated)

8 week review: full dose - peg 180mcg sc weekly and ribavirin

10 week review: review

ie. aim for full dose by 2 months: slower if clinical [side effects] or lab concern

Monthly HCV viral load to assess viral kinetic response and balance to side effect profile

Aimed for Ribavirin [Copegus] dose:

Genotype 1, 4, 5 or 6

weight <75kg 600mg am, 400mg pm

weight >75kg 600mg bd

Genotype 2 or 3

400mg bd

Dose issues: Any clinical/ laboratory signs of hepatic decompensation stop therapy and consult consultant

Platelets <20 Withhold therapy
Platelets 20-30 consider drop Pegylated interferon by 45mcg

Hb 10 or below drop Ribavirin by 200mg daily
If symptomatic with Hb>10 consider drop back 200mg Ribavirin

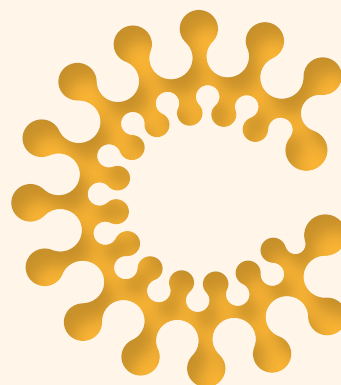
Consider use of EPO if >1 dose reduction
Stop Pegylated interferon if clinical infection

WCC <0.75 / ANC < 0.4 if Patient well / stable monitor 2 weekly.

If patient not stable consider dropping back Pegylated interferon to half dose/omit.

EPO protocol 10,000IU s/c weekly pre-treatment and titrate to Hb increase by 10,000IU/ weekly until HB >10.

GCSF – consider weekly if WCC <0.75 after one dose reduction



Summary: Patients with decompensated cirrhosis

48 weeks of ribavirin and Pegylated IFN (2A or 2B) in a centre with experience in the management of these patients, possibly using LADR.

Retreating patients who have previously failed therapy

Recently the EPIC3 trial has reported the effectiveness of retreating patients who have previously failed to achieve an SVR using combination IFN (non-Pegylated in 60%) and Ribavirin.¹⁹ This multicentre study used 48 weeks of PEGylated IFN2B with Ribavirin. Patients had viral load measured at 12 weeks & treatment was stopped for those not achieving complete EVR. The SVR was significantly affected by previous treatment regime, response to treatment, genotype and fibrosis stage (see table below).

The benefits of re-treatment need to be discussed individually with patients and based on previous side effect profiles, chance of developing advanced fibrosis/complications of liver disease & chance of SVR. Decision to retreat must be based on individual patients, although treatment is unlikely to be worthwhile in patients with a predicted SVR below 25% unless there is cirrhosis & a high risk of decompensation when the lower success rate might be cost effective.

A second large study (REPEAT)²⁰ investigated the effectiveness of Pegylated IFN 2A in re-treatment of primary non-responders to Pegylated IFN2B. This study used high induction doses of IFN (360µg weekly - above licensed doses). The overall SVR was 16% and therefore this high dose induction regime is not recommended.

However it should be noted that this study had a much harder to treat population than the EPIC3 study (91% genotype 1 and a high proportion of cirrhotics). A smaller study of genotype 2 and 3 patients using 48 weeks of standard dose therapy showed more favourable results for PEG IFN2A (comparable to the EPIC3 results) and this may be considered in individual cases.²¹

Summary: Retreating patients with have previously failed therapy

Repeat treatment should be considered based on the likelihood of treatment success, clinically important liver disease and side effects of treatment on a case by case basis. Where treatment is used it should usually be 48 weeks of weight based ribavirin and Pegylated IFN2B (1.5 µg / kg weekly). Treatment should be stopped at week 16 if the patient does not achieve a negative PCR at week 12.

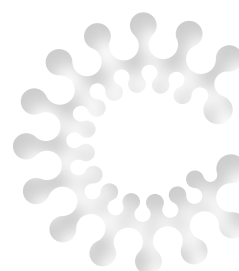


Table: Expected results of re-treatment (from EPIC3 study)

Previous Rx	Primary non-responder			Relapser responder		
	PEG2b	PEG2a	IFN [‡]	PEG2b	PEG2a	IFN [‡]
G1 F2 *	8%	4%	18%	37%	27%	42%
G1 F3	4%	2%	16%	29%	10%	28%
G1 F4	5%	2%	8%	18%	20%	26%
G2/3 F2	57%	50%	68%	75%	50%	76%
G2/3 F3	50%	33%	39%	63%	62%	67%
G2/3 F4	0%	33%	40%	36%	58%	59%
G4 F2	-	50%	33%	-	100%	100%
G4 F3	0%	-	0%	-	0%	100%
G4 F4	0%	-	14%	50%	100%	75%
All patients	7%	6%	11%	32%	34%	43%

* genotype and fibrosis score by Metavir

‡ Non-Pegylated IFN

Protocols for managing treatment side effects

Many patients on treatment with Pegylated IFN and ribavirin suffer significant treatment related adverse effects. These range from mild skin rashes and irritability to severe depression and blood dyscrasias. Most side effects need management on a case by case basis that may need dose alteration or treatment cessation dependent on severity. Evidence exists for management of depression, anaemia and leucopenia

Depression

Depression is common on treatment. A recent prospective study confirmed that Citalopram effectively reduces depression scores for patients developing depression during therapy.²² Treatment should be considered for patients with significant depressive side effects not already on psychoactive medication and continued until at least three months after the end of antiviral treatment

Anaemia

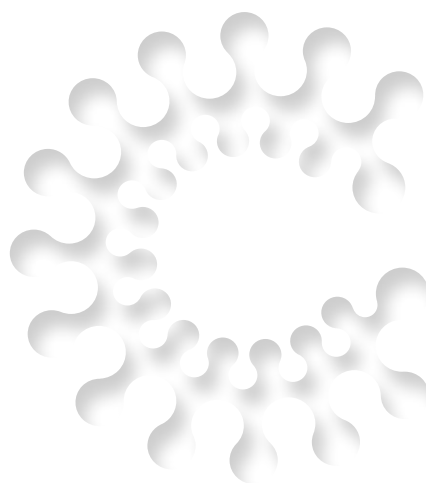
Ribavirin frequently causes anaemia of variable severity, through a number of mechanisms²³. Management of anaemia depends on the haemoglobin level and patient symptoms. Patients whose haemoglobin falls below 10 g / l or with severe anaemia associated symptoms should have their daily dose of ribavirin reduced by 200mg as per the treatment licence. Ribavirin discontinuation should be considered for patients where the anaemia causes unacceptable side effects or where the haemoglobin falls below 8.5 g / l despite dose alteration. It is especially important to minimise ribavirin dose reductions prior to week 12 as this has the most effect on SVR.

However as ribavirin dose reduction is associated with reduced SVR, patients requiring more than one dose ribavirin dose reduction should be considered for treatment with erythropoietin (up to 40,000 units weekly). This has been shown effective in RCTs at preventing large dose reductions / treatment discontinuation^{24,25} and thus maximising SVR rates.

This approach has not been considered by NICE (as this guidance did not include management of side-effects) in England but is recommended in the SIGN guidance (published on the same year but covering side-effect management) covering Scotland. This will require funding approval from the PCTs.

Leucopenia

Interferon frequently causes leucopenia. Treatment reduction schedules as per product licences are given in the table below. For patients with persistently low neutrophil counts despite a first dose reduction Filgastrim (Granulocyte colony stimulating factor) may achieve improvements in white cell count that allow treatment not to be interrupted. Filgastrim (105mcg weekly) should be considered in all patients where more than a single dose alteration is considered for interferon associated neutropenia. This approach has not been considered by NICE (as this guidance did not include management of side-effects) in England but is recommended in the SIGN guidance (published on the same year but covering side-effect management) covering Scotland. This will require funding approval from the PCTs. This will require PCT funding.



Summary: Protocols for treatment alterations for haematological abnormalities

Neutrophils

Initially <0.75

Reduce IFN dose by up to 50%

Repeat FBC @ 1 Week

Then...

Neutrophils >0.75

Restart full IFN dose

Neutrophils <0.75

GCSF weekly

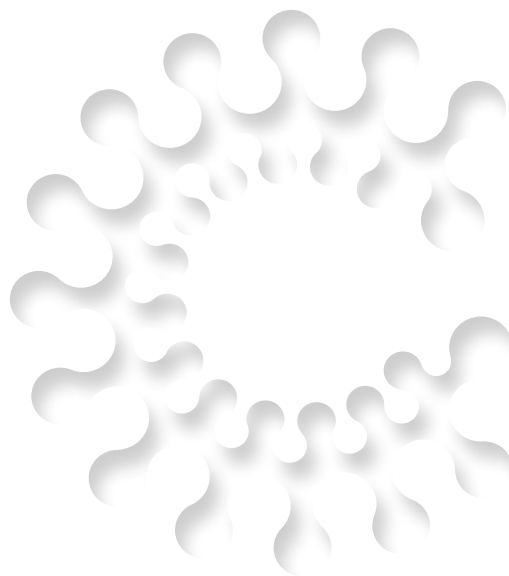
Patients on GCSF (105 μgm weekly)

Weekly FBC for 4 weeks

If neutrophils > 0.75 return to full dose IFN

If neutrophils < 0.75 , remain on reduced dose IFN

If neutrophils < 0.5 , stop treatment



Platelets

< 50 50% IFN dose reduction

Repeat FBC @ 1 week

< 25 consider stopping treatment

Haemoglobin

Hb >10 , no symptoms

no dose alternation

Hb <10 or Hb 2g fall in 4 weeks or severe symptoms

Ribavirin 200mg daily

Repeat FBC weekly and repeat as required

Consider EPO for any patient needing more than one dose alteration

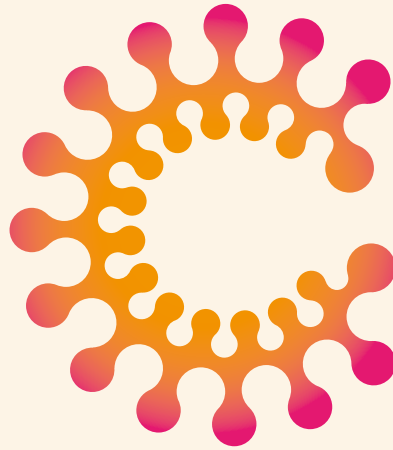
Hb < 8.5

consider ending ribavirin

Once Hb stable, repeat after 2 week then return to standard monitoring

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Hepatitis C

Greater Manchester Hepatitis C Strategy

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