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Review article: Optimising SVR and the management of haematological side effects of peginterferon/ribavirin antiviral therapy for HCV: The role of Epoetin,G-CSF and novel agents

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Review article: Optimising SVR and the management of haematological side effects of peginterferon/ribavirin antiviral therapy for HCV: The role of Epoetin, G-CSF and novel agents

MacNicholas R. , Norris S.

Abstract

Background:

Chronic hepatitis C is one of the leading causes for chronic liver disease globally. The past two decades have seen many advances in hepatitis C treatment. Despite these advances side effects of treatment are common. Haematological complications of treatment can result in treatment cessation and suboptimal results. Recent data has suggested a role for Epoetin/G-CSF in optimising SVR.

Aim:

To investigate the nature, frequency and management of haematological side effects in the treatment of chronic hepatitis C infection.

Methods:

The terms hepatitis C, HCV, treatment, side effects, Interferon, PegInterferon, Ribavirin, anaemia, haemoglobin, neutropaenia, thrombocytopaenia, haematological, growth factor, erythropoietin, granulocyte colony stimulating factor were searched on MEDLINE from 1991-2009. References from selected articles were also included.

Results:

Haematological side effects such as anaemia, neutropaenia and thrombocytopaenia are frequent in anti-HCV treatment. The off-label use of haematological growth factors is common and effective.

Conclusions:

Erythropoietic agents are effective in treating anaemia, preventing ribavirin dose reduction, improving patients' quality of life but the effect on SVR is not fully elucidated. G-CSF is effective in raising ANC, however neutropaenic HCV-infected patients on combination treatment may not experience increased bacterial infections. Eltrombopag a new oral thrombopoietin mimetic may allow combination treatment in patients with thrombocytopaenia..

Background

Hepatitis C virus (HCV) is a single stranded RNA virus belonging to the Flaviviridae family and Flavivirus genus. After initial infection the virus persists in approximately 50-80% of individuals resulting in an estimated 170 million persons globally with chronic infection. HCV infection can progress to cirrhosis and hepatocellular carcinoma and is the leading indication for liver transplants in the United States. The current treatment for chronic HCV infection is peginterferon and ribavirin^{1,2}.

The primary goal of HCV therapy is viral clearance thereby reducing the risk of progression to end-stage liver disease and hepatocellular carcinoma and improving quality of life. In practice viral eradication is characterised by a sustained virological response (SVR) defined as the absence of HCV RNA in serum determined by a sensitive test at the end of treatment and 6 months later.

An SVR rate of 42-46% is seen in genotype 1 HCV-infected patients while an SVR rate of 76-82% is seen in those with genotypes 2 and 3^{1,2}. The favourable SVR rates in genotypes 2 and 3 have led to shorter treatment regimens in these genotypes and conversely longer regimens in genotypes with poorer responses.

Unfortunately, despite major advances in HCV treatment, the combination of interferon and ribavirin results in side effects necessitating dose reduction or cessation in up to 32%¹. Common side effects include flu-like symptoms, depression, autoimmune disorders and haematological complications such as anaemia, neutropaenia and thrombocytopaenia (see table 1).

Frequency of Adverse Events for Peginterferon Alpha-2a and Ribavirin (>20%)

Fatigue	54%	Irritability	24%
Headache	47%	Arthralgia	27%
Pyrexia	43%	Anorexia	21%
Myalgia	42%	Dermatitis	21%
Rigors	24%	Depression	22%
Insomnia	37%	Fatigue	54%
Nausea	29%	Alopecia	28%

Frequency of Adverse Events for Peginterferon Alpha-2a and Ribavirin (>20%)

	Peg-Interferon Alpha2a	Ribavirin
Adverse event	11%	21%
Laboratory abnormality	25%	24%
Anaemia	1%	22%
Neutropaenia	20%	4%
Thrombocytopaenia	4%	<1%

Adapted from
Fried et al. 1

Table 1.

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8 Dose reduction and premature discontinuation of therapy may result in suboptimal
9 SVR rates^{3,4} highlighting the importance of addressing side effects. In recent years
10 pharmacological support to reduce haematological side effects has become common
11 practice. A recent French study reported that 46% of clinicians treating HCV infection
12 used erythropoietic agents and granulocyte colony stimulating factor but there was
13 considerable variation in the molecules and regimens used⁵. These haematological
14 supports are costly and not without side effects. The impact of these therapies on
15 SVR rates remains to be clarified.
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23 Aims

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26 To investigate the nature, frequency and management of haematological side effects
27 in the treatment of chronic hepatitis C infection.
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31 Methods

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35 The National Library of Medicine Medline literature search engine (PubMed)
36 database was searched for the period between 1991(FDA approval of alpha) and
37 2009. Search terms included: hepatitis C, HCV, treatment, side effects, Interferon,
38 PegInterferon, Ribavirin, anaemia, haemoglobin, neutropaenia, thrombocytopenia,
39 haematological, growth factor, erythropoietin, granulocyte colony stimulating factor.
40 Key articles were identified and reviewed. Relevant references cited were also
41 reviewed and the hyperlink *Other related articles* in PubMed was used to extend the
42 search. Abstracts from EASL and AASLD meetings were also reviewed.
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48 Results

49 *Anaemia*

50 *NATURE*

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58 Although ribavirin induces a dose-dependent haemolytic anaemia, the underlying
59 mechanism is poorly understood. Ribavirin concentrates in erythrocytes⁶ causing
60 inhibition of intracellular energy metabolism and oxidative membrane damage, which

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3 ultimately leads to an accelerated extravascular haemolysis by the reticulo-
4 endothelial system⁷. Ribavirin-induced haemolysis overwhelms reticulocytosis,
5 resulting in anaemia⁸. Furthermore, reticulocytosis in response to ribavirin-induced
6 haemolysis is also impaired by peginterferon induced bone marrow suppression,
7 which exacerbates declining haemoglobin levels⁹. However, the majority of observed
8 haemoglobin reductions are secondary to ribavirin.
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12 13 14 *FREQUENCY*

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16
17 Anaemia is diagnosed by specific laboratory values based on gender and age. The
18 World Health Organisation defines anaemia as haemoglobin levels <13g/dL in men
19 and <12g/dL in women. Anaemia occurs in up to 36% of patients receiving pegylated
20 interferon and ribavirin combination therapy^{1,10}. Haemoglobin reductions below
21 10g/dL and 8.5g/dL occur in approximately 20% and 5% of patients respectively. The
22 majority of the haemoglobin decline occurs within the first four weeks of treatment
23 and is more severe with ribavirin doses of 800mg or greater. Although anaemia is
24 dose-dependent, the discrepancy between plasma and erythrocyte concentrations of
25 ribavirin and the development of anaemia points towards additional factors⁷. Female
26 gender, age >60, higher ribavirin dose by body weight (12mg/kg or more), the rate of
27 haemoglobin reduction at week two, Asian race and a reduced creatinine clearance
28 are predictors of the development of anaemia with anti-HCV therapy^{11,12}. In patients
29 with chronic liver disease anaemia of chronic disease has been identified in 30% to
30 70%¹³; iron deficiency should also be identified and corrected prior to treatment.
31 Identifying patients with pre-existing anaemia and those at high risk of developing
32 anaemia during treatment facilitates the individualisation of anti-HCV therapy with
33 lower ribavirin dosing or earlier growth factor support. For example, HCV treatment
34 regimens with ribavirin are contraindicated in patients with renal failure but a recent
35 small study using peginterferon and low dose ribavirin (200mg) in dialysis patients
36 has achieved an SVR rate of 28.6%¹⁴.
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49 *EFFECT OF ANAEMIA*

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51 Anaemia can have negative effects on both cerebral function and quality of life and
52 in many chronic diseases is associated with an increased morbidity and mortality.
53 The presence of haemoglobin <8.0g/dL in patients undergoing dialysis predicts a
54 two-fold increase in mortality when compared with haemoglobin levels between 10.0
55 and 11.0 g/dL¹⁵. In patients with congestive heart failure anaemia is an independent
56 predictor of subsequent death with every 1% decrease in haematocrit increasing
57 mortality by 1.6%¹⁶. Management of anaemia in these groups can reduce mortality.
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3 Lower haemoglobin levels also adversely affect morbidity and quality of life in these
4 groups^{17,18,19}.

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7 In HCV treatment patients who are in general younger and without co-morbid illness
8 the effect of anaemia on mortality is unknown however morbidity is common.
9 Anaemia during combination therapy is an independent factor in reduction of health-
10 related quality of life scores (HRQL)²⁰. Mean HRQL scores of anaemic patients on
11 combination therapy are significantly lower than patients with other chronic
12 conditions and the general population; improvement of anaemia with epoetin alpha
13 can provide significant improvement in these scores²¹.
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19 *EFFECT OF RIBAVIRIN ON SVR*

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21 Anaemia is by far the most frequent cause of discontinuation of combination
22 treatment, being cited in up to 36% of patients who discontinue therapy early¹⁰.
23 Current recommendations for management of anaemia in treatment patients suggest
24 a ribavirin dose reduction to 600mg daily when haemoglobin falls to <10g/dL and
25 discontinuation when <8.5g/dL^{2,22}.
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29 While these recommendations are based on evidence from randomised controlled
30 trials, in practice there is a wide variation in individual tolerance of anaemia. Factors
31 such as rapidity of the fall in haemoglobin, presence of co-morbid illness and the
32 patient's age all play a role in determining the need for ribavirin dosage reduction. An
33 asymptomatic, young, healthy patient with a haemoglobin of 9.0g/dL for example
34 may not require reduction of ribavirin dose (figure 1).
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38 The positive correlation between higher early maintenance doses of ribavirin and
39 achievement of an SVR also discourages dose reduction particularly in an
40 asymptomatic anaemic patient. Patients on combination therapy who receive greater
41 than 80% of ribavirin and interferon over 24-48 weeks have significantly higher SVR
42 rates than those who took less than 80%³. It was unclear whether this 80%
43 represented a dose reduction during the course of treatment or temporary
44 interruption of treatment or whether changes in peginterferon or ribavirin caused the
45 reduction in SVR. SVR was most affected by changes to the regimen within the first
46 12 weeks.
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51 Reducing the dose of peginterferon alpha-2a or ribavirin after the first 20 weeks of
52 treatment to less than 60% recommended dose did not significantly effect virological
53 response at week 20 or SVR rates but a comparable reduction in ribavirin dose
54 during these early weeks reduced week 20 virologic response (38% to 26%; $P =$
55 0.041) and SVR (21% to 11%; $P = 0.031$)²³. Reducing the dose of either drug after
56 week 20 when HCV RNA was undetectable had no effect on SVR.
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Another study examined the effect of peginterferon alfa-2a and ribavirin dose
reductions in genotype 1 infected patients²⁴. EVR and SVR were not affected by

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3 ribavirin reductions when cumulative ribavirin exposure was >60%. However,
4 patients who received <60% of cumulative dose ribavirin, experienced prolonged
5 periods of ribavirin dose reduction, temporary interruptions and premature cessation
6 had significantly reduced SVR. More recently, the cumulative ribavirin dose to week
7 12 has been shown to be significantly associated with EVR and SVR in genotype 1
8 patients²⁵.
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12 Bronowicki et al²⁶ investigated the consequence of ribavirin cessation in patients
13 infected with genotype 1 hepatitis C who cleared HCV RNA at week 24. They
14 randomised patients to either combination therapy after 24 weeks or peginteron
15 alpha-2a alone. Patients who stopped ribavirin had significantly higher viral
16 breakthroughs and SVR was reduced (52.8% vs. 68.2%; p=0.004). However,
17 stopping ribavirin at 24 weeks in patients who had experienced a rapid virological
18 response did not affect SVR.
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22 Similar data was also generated by the IDEAL study²⁷ which compared the rate of
23 adverse events, safety profile and SVR among three groups: (1) peginterferon alfa-
24 2b 1.5µg/kg per week + ribavirin 800-1400mg per day, (2) peginterferon alfa-2b
25 1.0µg/kg weekly + ribavirin 800-1400mg per day and (3) peginterferon-alfa2a 180
26 µg/kg per week + ribavirin 1000-1200mg per day. Increased exposure to ribavirin
27 was associated with an increased likelihood of SVR. Although anaemia requiring
28 dose reduction and or erythropoietin occurred in 28% of all patients this did not
29 reduce the SVR. In fact, patients with anaemia needing ribavirin dose reduction had
30 a higher rate of SVR even when the ribavirin was reduced by as much as 50%.
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34 The phase II HCV SPRINT-1²⁸ study investigated the safety and efficacy of
35 boceprevir (a novel HCV protease inhibitor) in various combinations with
36 peginterferon alfa-2b and ribavirin. The addition of boceprevir with a lead in period
37 significantly improved SVR. However, one half of the boceprevir and one third of the
38 standard treatment group (no boceprevir exposure) developed anaemia requiring
39 epoetin in 39-51% and 26%, respectively. Phase III studies are awaited.
40 Interestingly, the development of anaemia was again noted to correlate significantly
41 with an increase in SVR.
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49 Although haemoglobin levels characteristically stabilise by the second month of HCV
50 therapy without epoetin therapy¹, many clinicians use erythropoietic agents in an
51 attempt to maintain ribavirin doses particularly in the first 12 weeks of treatment.
52 However the routine use of erythropoietin in all patients at the initiation of
53 combination treatment does not appear to improve SVR²⁹.
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56 *MANAGEMENT OF ANAEMIA*

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59 Erythropoietin is a glycoprotein hormone that controls erythropoiesis. It is primarily
60 synthesised in the renal cortex with a small amount produced in the liver. Production
of erythropoietin in response to reduced blood oxygen availability leads to up-

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3 regulation of red cell production. Three erythropoietic agents are currently available:
4 epoetin alpha, epoetin beta, and darbepoetin alpha. Their use in HCV treatment is
5 currently off-label. Recombinant human erythropoietin (epoetin alpha) is the
6 genetically engineered form of the hormone erythropoietin and has been extensively
7 studied in chronic renal disease. Side effects such as headaches, nausea, arthralgia,
8 polycythaemia, cerebrovascular accidents, hypertension and myocardial infarction
9 and pure red cell aplasia are well documented. Myocardial infarction and
10 cerebrovascular accidents are rare complications in non-renal populations and
11 recent studies have not shown HCV treatment patients to be at increased risk³⁰.
12 However, there are several reports of antibody-mediated pure red cell aplasia
13 associated with erythropoietic agents during HCV treatment^{31,32}.

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20 There are concerns that erythropoietin may worsen outcomes in patients with cancer
21 The use of erythropoietin in patients with metastatic breast cancer receiving first line
22 chemotherapy leads to decreased survival³³. Patients with head and neck cancer
23 receiving radiotherapy have poorer locoregional progression-free survival with
24 epoetin beta than with placebo³⁴. One of the possible mechanisms for these findings
25 is promotion of angiogenesis by erythropoietin. This may occur in tumours with or
26 without erythropoietin receptors³⁵. As hepatocellular carcinoma is an angiogenesis
27 dependant cancer treatment with erythropoietin (especially in cirrhotics) may
28 promote tumour growth, however there is no evidence at the present time to support
29 this.
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36 Of the agents available, epoetin alpha has been the agent commonly used in anti-
37 HCV treatments. Afdhal et al demonstrated that epoetin alpha given once weekly
38 (40,000U subcutaneously) maintained ribavirin in 88% of patients vs. 60% of patients
39 receiving placebo³⁶. Haemoglobin increased by an average of 2.2 g/dL in the
40 epoetin group vs. 0.1 g/dL in the placebo group ($P < 0.001$). Dieterich et al³⁷
41 compared epoetin alpha treatment for anaemia (haemoglobin < 12 g/dL) with standard
42 of care and found significantly higher haemoglobin levels (13.8g/dL vs. 11.4g/dL,
43 $p < 0.011$) in the treatment group at week 16 of epoetin alpha. Reductions in ribavirin
44 dose at week 4 were significantly lower in the treatment group ($p < 0.011$) and 83% of
45 the treatment group maintained ribavirin doses of 800mg/day or more compared with
46 54% of the standard of care group. Epoetin alpha was reported to be well tolerated.
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51 Darbepoetin is a modified version of epoetin that has a three-fold longer serum half-
52 life. Younossi et al³⁸ recently conducted a phase II study using darbepoetin alpha.
53 Patients received pegylated interferon alpha-2b (1.5 mug/kg once weekly) and
54 ribavirin (800-1400 mg once daily) and anaemic patients (haemoglobin < 10.5 g/dL)
55 received darbepoetin alpha (3 mug/kg once every 2 weeks) with a dose titration to
56 achieve haemoglobin > 12.0 g/dL. After 81 days of darbepoetin alpha, haemoglobin
57 increased by 1.9 +/- 1.0 g/dL to 12.1 +/- 1.1 g/dL ($P < 0.0001$). The introduction of
58 viramidine (a prodrug of ribavirin) which is associated with less haemolytic anaemia
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3 may eliminate the need for these medications in the future³⁹. The use of
4 erythropoietic growth factors during HCV combination therapy also appears to be
5 cost-effective for genotypes 1, 2, or 3⁴⁰.
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8 Despite the beneficial effects of epoetin on anaemia, its effect on SVR is less clear.
9 Kuglemaš et al⁴¹ compared standard therapy with peginterferon alfa2b and weight-
10 based ribavirin with an adjuvant treatment of anaemia and neutropaenia. Anaemia
11 was treated with darbepoetin alfa (3mcg/kg twice weekly) when haemoglobin fell
12 <12g/dL or <75% from baseline. Neutropaenia was treated with filgrastim. The study
13 was powered to show a 22% difference in SVR in favour of adjuvant treatment,
14 however there was no difference in SVR between the two treatment groups³⁸.
15 Furthermore, a retrospective study of 132 HCV patients also failed to show a
16 significant difference in SVR rates with the use of growth factors⁴².
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21 Shiffman et al⁴³ randomised 150 treatment-naive patients with chronic HCV
22 genotype 1 into 3 treatment groups: (1) peginterferon alpha-2b (1.5 microg/kg/week)
23 and weight-based ribavirin 13.3 mg/kg/day (800 to 1400 mg/day); (2) Peginterferon
24 alpha-2b and weight-based ribavirin and epoetin (40,000 U/week); or (3)
25 peginterferon alpha-2b and higher dose weight-based ribavirin 15.2 mg/kg/day (1000
26 to 1600 mg/day) and epoetin. Epoetin was started at initiation of therapy and ribavirin
27 was reduced in decrements of 200mg if required. Declines in haemoglobin to less
28 than 10g/dL were significantly less frequent in group 2 than group 1 (10% vs. 40%
29 p<0.05). SVR was significantly increased in group 3 (49%, p<0.05) mostly by a
30 reduction in relapses. However there was no significant difference in SVR among
31 groups 1 and 2 (19% vs. 29%). The routine use of epoetin in all patients at the start
32 of treatment does not appear to be beneficial; however a higher dose of ribavirin at
33 initiation of treatment increases SVR by reducing relapse rates.
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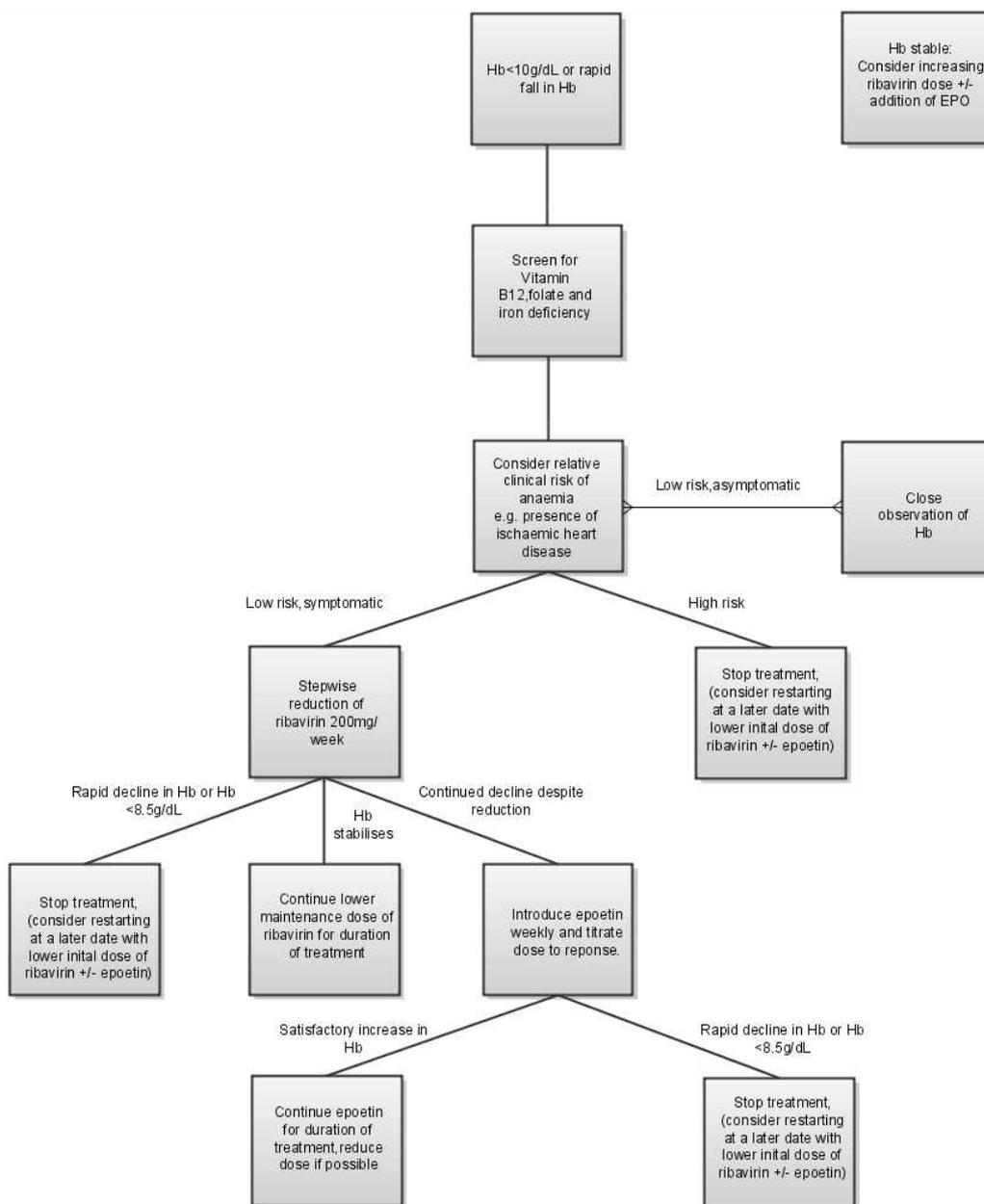


Figure 1. Suggested algorithm for approaching anaemia

Neutropaenia

NATURE

Granulocyte colony stimulating factor (G-CSF) is a cytokine produced by monocytes, macrophages, endothelial cells, and fibroblasts in response to such agents as endotoxin, TNF, IL-1, phorbol esters, GM-CSF, IL-3, IL-4 and γ -interferon⁴⁴. G-CSF maintains basal neutrophil counts and generates neutrophilia in response to infections⁴⁵. Neutropaenia is defined as a peripheral absolute neutrophil count below $1.5 \times 10^9/L$. With typical doses of peginterferon used in HCV therapy the absolute neutrophil count (ANC) often decreases by 30-50% from baseline^{10,40,46,47}. Neutropaenia is a common reason for interferon/peginterferon dose reduction or withdrawal in clinical trials^{1,2}. Defective synthesis of endogenous G-CSF during combination treatment may contribute to neutropaenia⁴⁸.

FREQUENCY & EFFECT

In a retrospective cohort analysis of 119 patients receiving anti-HCV therapy, factors associated with neutropaenia and its clinical consequences were reported - neutrophil counts decreased by an average of 34% (range +21% to -71%) however interferon alpha was not reduced⁴⁹. In total, 22 patients (18%) developed bacterial infections but none of the 22 patients were neutropaenic. Juarez-Navarro et al⁵⁰ reported on haematological toxicities in 209 patients receiving pegylated interferon-alpha2a (180 μ g/week) plus ribavirin (800 mg/day for 24 weeks in cases of nongenotype 1, or 1000-1200 mg/day for 48 weeks for genotype 1, according to whether patients weighed more or less than 75 kg). 95 patients developed neutropaenia with absolute neutrophil count (ANC) $<1500/\mu L$ (mean 1100 \pm 250 cells/ μL), but reported no increased risk of infection. Despite these findings, neutropaenia is a common reason for dose reduction or withdrawal of interferon or peginterferon in clinical trials in HCV^{1,2,51}.

MANAGEMENT OF NEUTROPAENIA

G-CSF is commonly used in primary prevention of febrile neutropaenia (FN) following chemotherapy where it has been shown to reduce its occurrence and to reduce early deaths, including infection-related mortality⁵². The mortality rates associated with FN in these patients ranges from 2 to 21%. Not all drug induced neutropaenias are alike, having different clinical consequences and response to g-csf⁵³. It is unlikely that HCV treatment patients who experience Interferon-induced neutropaenia are at the same risk for bacterial infection as oncology patients with chemotherapy-induced neutropaenia,.

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10 many clinicians treating HCV infection support the absolute neutrophil count with G-
11 CSF. Unfortunately, guidelines for adjustment of interferon in the face of
12 neutropaenia are unclear with three large studies failing to suggest a specific
13 absolute neutrophil count which would trigger supportive treatment^{1,2,22}.

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16 Filgrastim, lenograstim and nartograstim are recombinant versions of human
17 granulocyte colony stimulating factor (rhG-CSF). They are approved for use in
18 chemotherapy-induced neutropaenia and are used off-label in HCV therapy. In 2002
19 the FDA also approved a pegylated version of filgrastim for the treatment of febrile
20 neutropaenia.
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23
24 G-CSF can cause bone pain, rashes, pruritus, fevers and gastrointestinal upset.
25 Rare side effects noted in bone marrow transplants include pyogenic infections,
26 leukocytoclastic vasculitis, interstitial pneumonitis, anaphylaxis and splenic rupture.
27 The impact of G-CSF on SVR rates remains unclear with few studies investigating
28 an association.
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32 Koirala et al⁵⁴ retrospectively reviewed 163 patients who received combination
33 therapy for HCV. They identified 30 patients treated with G-CSF for neutropaenia
34 (defined in this study as $ANC \leq 1.0 \times 10^9/L$) and matched them with a group who
35 received anti-HCV treatment without developing neutropaenia. The ANC fell $\leq 1.0 \times$
36 $10^9/L$ after an average of 13 weeks (range 2-49 ± 10 weeks). G-CSF was given
37 weekly at a dose of 300 μ g giving an average rise in ANC of $3.9 \times 10^9/L$. Eight
38 patients required dose escalation, two required dose reduction and one stopped due
39 to side effects (rash). There was no statistically significant difference in the SVR
40 between the two groups (61% vs. 76%, $P = 0.18$).
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44
45 Younossi et al³⁵ conducted a phase II clinical trial to assess dose, efficacy and
46 safety of darbepoetin alpha and filgrastim for treatment of anaemia and neutropaenia
47 associated in HCV treatment patients on combination therapy. 101 patients were
48 treated with pegylated interferon alpha-2b (1.5 μ g/kg once weekly) and ribavirin
49 (800-1400 mg once daily). Patients with haemoglobin ≤ 10.5 g/dL received
50 darbepoetin alpha (3 μ g/kg once every 2 weeks); the dose was titrated to achieve a
51 haemoglobin level of 12.0 g/dL. Patients with neutropaenia ($ANC \leq 0.75 \times 10^9/L$)
52 received filgrastim with the dose titrated from 150 μ g weekly to 300 μ g thrice weekly
53 to maintain $ANC \geq 0.75 \times 10^9/L$ and $< 10 \times 10^9/L$. 52% of patients required
54 darbepoetin alpha, filgrastim or both. Filgrastim raised ANC from $0.75 \pm 0.16 \times 10^9/L$
55 to $8.28 \pm 5.67 \times 10^9/L$ ($P < 0.0001$). No significant adverse events were observed.
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57 Treatment with growth factors was independently associated with an SVR.
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Thrombocytopenia

Decreases in platelet counts necessitating interferon dose reduction are observed in less than 4% of patients on combination therapy¹. Thrombotic purpura has been seen as a rare complication of combination treatment⁵⁵. However, thrombocytopenia associated with chronic liver disease may prevent initiation of treatment. In a phase 2 study eltrombopag, an oral thrombopoietin mimetic has been shown to increase platelet counts in HCV-related cirrhosis⁵⁶. 74 patients with platelet counts of $20-70 \times 10^3 / \text{mm}^3$ were randomly assigned to receive eltrombopag (30, 50, or 75 mg daily) or placebo daily for 4 weeks. At week 4, none of the controls had an increase in platelets compared with 75-95% of those receiving eltrombopag doses of 30-75mg respectively. Twelve weeks of antiviral therapy, with concurrent receipt of eltrombopag or placebo, were completed by 36%, 53%, and 65% of patients receiving 30 mg, 50 mg, and 75 mg of eltrombopag, respectively, and by 6% of patients in the placebo group. The most common side effect was headache. Phase 3 studies are awaited to reveal the impact of eltrombopag on SVR rates.

Conclusions

Despite major advances in HCV treatment, the combination of interferon and ribavirin results in side effects such as flu-like symptoms, depression, and haematological complications such as anaemia, neutropenia and thrombocytopenia, necessitating dose reduction or cessation in up to 32% of treated patients. Consequently, the off-label use of haematological growth factors in the treatment of chronic hepatitis C is common. Erythropoietic agents are effective in treating anaemia and preventing ribavirin dose reduction, and can improve patients' quality of life but a positive impact on SVR is not substantiated by studies to date. G-CSF is effective in raising ANC, however there is a lack of evidence that neutropenic HCV-infected patients on combination treatment experience increased bacterial infections. Eltrombopag, a new oral thrombopoietin mimetic, may allow combination treatment in patients with thrombocytopenia although further data are required.

Summary and Recommendations

Peginterferon initiates a virological response and ribavirin reduces relapse

Reducing the dose of interferon below 80% reduces virological response but reducing the dose of ribavirin particularly when HCV RNA is undetectable has no effect on SVR

Interrupting ribavirin leads to falls in SVR

The use of epoetin alfa has not been shown to enhance SVR

Some patients may not be able to tolerate ribavirin without concomitant erythropoietin

Neutropaenia secondary to peginterferon/ribavirin therapy has not been shown to increase the risk of bacterial infections. Consequently there is no absolute ANC below which supportive therapy should be instigated.

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