Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Ribavirin

GENERAL INFORMATION

The synthetic triazole nucleoside, ribavirin (1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, tribavirin, virazole), has a broad spectrum of antiviral activity, including DNA as well as RNA viruses. Ribavirin closely resembles guanosine and is converted intracellularly to mono-, di-, and triphosphate derivatives, which inhibit virally induced enzymes involved in viral nucleic acid synthesis [1]. Of the DNA viruses, ribavirin is active against *Herpes simplex* virus and hepatitis B virus; among the RNA viruses, good activity has been observed against hepatitis C virus, orthomyxoviruses, paramyxoviruses, arenaviruses, and bunyaviruses. Although active against HIV in vitro and in vivo [2], ribavirin is not widely used in the treatment of HIV infection.

Oral ribavirin has been successfully used in the treatment of Lassa fever [3], Crimean Congo hemorrhagic fever [4], and in combination therapy with interferon alfa for hepatitis C infection [5]. Several publications have suggested enhanced efficacy of the combination of interferon alfa with ribavirin when compared with monotherapy with interferon alfa. There is also evidence that re-treatment with the combination may succeed in controlling or eliminating viremia when monotherapy has failed. Although the combination may lead to some increase in the adverse reactions normally associated with interferon alfa (dyspnea, pharyngitis, pruritus, nausea, insomnia, and anorexia) [6], there is no doubt that oral ribavirin adds to the overall toxicity of the combination by causing hemolytic anemia, which is usually mild.

Ribavirin is well absorbed orally, but it can be given in aerosol form for the treatment of respiratory syncytial virus (RSV) infections in immunocompromised patients, and in those with cardiopulmonary abnormalities, or in infants receiving mechanical ventilation [7,8].

General adverse effects and adverse reactions

Adverse reactions to interferon and ribavirin in the treatment of hepatitis C infection have been reviewed [9]. Since ribavirin is almost always used in combination with interferons, it can be difficult to know whether adverse events, if drug-induced, are due to one or the other. In many cases authors do not even discuss this problem, often attributing the supposed adverse reactions to the interferon. In some cases withdrawal of one of the agents can provide evidence, and in other cases there may be other clues. For example, in cases of skin pigmentation at the site of injection of interferons, the adverse reaction may be presumed to be due to interferon [10], a type II between-the-eyes adverse reaction [11]. In one case hemolytic anemia was attributed to interferon rather than ribavirin because the patient had previously taken a course of interferon without adverse reactions [12]; presumably the inference was that the patient had been sensitized by the previous course. A systematic review of cases in which the drugs were used together and individually can also yield useful information, as in the case of pneumonitis in patients being treated with interferon and ribavirin, attributed to interferon [13]. Similarly, in cases of ocular myasthenia [14], pleural effusion [15], and cataract [16] the interferon was blamed because no previous cases were found in association with ribavirin alone. In cases in which the adverse event persists for some time after the withdrawal of pegylated interferon and ribavirin, the long half of peginterferon is cited as a possible explanation, but this is weak evidence in such cases. In some cases it may be impossible to tell whether the adverse event, if drug-induced, was due to one or other of the drugs or to the combination.

DRUG STUDIES

Observational studies

Chronic hepatitis

The combination of interferon + ribavirin causes the same adverse reactions in patients who are co-infected with hepatitis C and HIV as in those who have hepatitis C only. However, in one series of 68 patients some unexpected adverse reactions were recorded [17]. One subject developed pancreatitis and four others developed asymptomatic hyperamylasemia, which disappeared after withdrawal. All of them were taking concomitant didanosine. Secondly, lactate concentrations increased slightly in two individuals, both of whom were taking stavudine. Significant weight loss (4.5 kg on average within 6 months) may be another adverse effect resulting from the interaction of ribavirin and HIV nucleoside analogues.

The mechanism of the beneficial effect of adding ribavirin to interferon is not fully understood. Ribavirin monotherapy is not effective in hepatitis C. However, adding ribavirin to interferon increases the number of patients with a virological response although it also increases the number of adverse events. Both the benefits and harms of adding ribavirin to interferon for patients with chronic hepatitis C should be considered before therapy is started.

Hepatitis C virus (HCV) RNA kinetics have been studied on day 1 in 15 patients (nine and six of genotypes 1 and non-1 respectively) and at weeks 1, 4, and 12 in 53 patients (19 and 34 of genotypes 1 and non-1 respectively) during treatment with ribavirin + pegylated interferon alfa-2a [18]. Patients with a sustained virological response (SVR) had a significantly more pronounced mean $\log_{10}$ decline from baseline in HCV RNA amounts at weeks 1 and 4 compared with patients who failed to achieve a sustained response, whereas there was no difference after day 1. For patients with a 2 $\log_{10}$ reduction in HCV RNA amounts on day 7, the positive predictive value for a sustained virological response was 92%, whereas week 12 was the best time point for predicting a later non-response in patients who failed to achieve a 2 $\log_{10}$ fall. In patients with genotype non-1 and a 2 $\log_{10}$ fall in HCV RNA amounts the positive predictive value for a sustained virological response was 89% at week 1, and 79% at weeks 4 and 12. The corresponding negative predictive values for

patients with genotype non-1 were 43%, 40%, and 100% respectively. Of the 60 patients, one withdrew from treatment after the second dose of pegylated interferon alfa-2a, four withdrew prematurely, one each at treatment weeks 8, 12, and 27 for unknown reasons, and one at week 16 for psychiatric reasons. One other patient withdrew at week 16 because of arthralgia. Dosage reduction was required in three patients because of thrombocytopenia or neutropenia, and in three others the dosage of ribavirin was reduced because of anemia.

Combination treatment of interferon-alfa + ribavirin for chronic hepatitis D does not induce virological responses at a sufficient rate, despite its partial effectiveness in improving biochemical responses, and is not superior to interferon-alfa monotherapy. Patients with chronic hepatitis D (n = 19) were treated with interferon alfa-2b (10 million U three times/week subcutaneously) and ribavirin (1000–1200 mg/day orally) for 24 months, with follow-up for at least 6 months (range 7–19) [19]. All had compensated liver disease, raised transaminase activities, and hepatitis D virus RNA positivity at baseline. Genotypic analyses showed hepatitis D virus genotype I and hepatitis B virus genotype D. There were biochemical responses in eight patients (42%) at the end of treatment and in seven patients (37%) at the end of follow-up. Only eight patients at the end of treatment and four at the end of follow-up had sustained virological responses. There were flu-like symptoms, generally mild or moderate, in most of the patients. Two patients required a short-term dosage reduction from 10 to 5 MU because of leukopenia and thrombocytopenia and two patients had a drop in hemoglobin, which was managed with a reduction in the dosage of ribavirin.

In two prospective, open trials in HIV/hepatitis C virus co-infected individuals who received peginterferon alfa-2b or alfa-2a + ribavirin for 48 weeks, responders were defined as those with a fall in hepatitis C virus RNA by at least 2 log units [20]. Of the 27 patients who developed psychiatric adverse reactions, 26 were responders and other adverse reactions, such as anemia and adverse reactions in the eyes, were also more frequent in responders. This suggests that the dosages may not have been high enough in the non-responders.

Prevention of recurrence after liver transplantation

It has been postulated that there is a risk of increased severity of recurrent hepatitis C virus infection in living donor liver transplantation (LDLT) patients. Preventive therapy for this has been studied in 23 patients [21]. All received interferon-alpha 2b and ribavirin 1 month after transplantation and for 12 months after the first negative HCV RNA test. They were then observed without therapy for 6 months (Group 1). Therapy was continued for at least 12 months when the HCV-RNA test remained positive (Group 2). They were removed from the protocol if they could not continue therapy for 12 months because of adverse reactions or could not start therapy because of early death. Eight patients were removed from the protocol (three died and two could not start because of their poor general condition). Nine patients were assigned to Group 1 and the other six to Group 2. The sustained virological response ratio was 39% (9/23). There was a significant difference between the groups in the histological activity score 1 year after therapy. No details were given of the adverse reactions in the eight patients who were withdrawn.

Fulminant hepatitis C

Pegylated interferon and ribavirin have been used successfully to treat fulminant hepatitis C infection; there were only mild self-limiting adverse reactions, such as hemolytic anemia [22].

Severe acute respiratory syndrome

High-dose ribavirin during an outbreak of severe acute respiratory syndrome in Toronto was associated with a high rate of adverse events: anemia (OR = 3.0; 99% CI = 1.5, 6.1), hypomagnesemia (OR = 21; 99% CI = 5.8, 73), and bradycardia (OR = 2.3; 99% CI = 1.0, 5.1) [23]. The risks of anemia, hypomagnesemia, and bradycardia attributable to ribavirin were 27%, 45%, and 17% respectively. The authors concluded that the use of high-dose ribavirin is appropriate only for the treatment of infectious diseases for which ribavirin has proven clinical efficacy, or in the context of a clinical trial. They further stated that ribavirin should not be used empirically for the treatment of viral syndromes of unknown origin.

In 16 patients taking ribavirin + peginterferon alfa-2b, nine patients reported flu-like symptoms, four developed anemia, three pancytopenia, three gastrointestinal symptoms, and one paresthesia, pruritus, and tremor [24]. All resolved after the end of treatment.

In a retrospective audit of 46 patients taking ribavirin + peginterferon alfa the following adverse events were reported: fatigue (85%), fever (83%), weight loss (80%), irritability (74%), and body pain (72%) [25].

Comparative studies

Two, large, randomized, placebo-controlled comparisons of interferon alfa-2b alone with the combination of interferon alfa-2b plus ribavirin have been published. In the initial treatment of chronic hepatitis C, 912 patients were randomly assigned to receive standard-dose interferon alfa-2b alone or in combination with ribavirin (1000 or 1200 mg/day orally, depending on body weight) for 24 or 48 weeks [5]. As expected, dosage reduction for anemia was necessary in 8% of patients taking the combination therapy and in none of those treated with interferon alone. Dyspnea, pharyngitis, pruritus, rash, nausea, insomnia, and anorexia were adverse effects that were reported more often during combination therapy with ribavirin [5]. In patients whose chronic hepatitis had relapsed after therapy with interferon alfa-2b alone, 345 patients were randomized to receive standard-dose interferon alfa-2b alone or in combination with ribavirin (1000 or 1200 mg/day orally, depending on body weight) for 6 months [6] Dosage reduction for anemia was required in 12/173 patients assigned to combination therapy and in

none assigned to interferon alone. As was the case in the initial therapy study, dyspnea, nausea, and rash were significantly more common in patients treated with the combination of interferon and ribavirin [6].

Ribavirin 15 mg/kg/day plus interferon alfa in 12 teenagers has been compared with interferon alone in 10 [26]. There was no difference in dropout rate, but viral clearance was achieved in 50% of the patients who took the combination treatment versus 30% of those who took monotherapy. Adverse events were similar in the two groups. There was mild hemolytic anemia at the end of the first month in most of the children who took ribavirin, but four had moderate to severe hemolysis and two had to stop taking ribavirin. Severe hemolysis in a patient with thalassemia warranted withdrawal of ribavirin within 3 months.

Systematic reviews

In a meta-analysis of 72 trials with a total of 9991 patients, ribavirin plus interferon significantly reduced morbidity plus mortality (OR = 0.46; 95% CI = 0.22, 0.96) and significantly improved sustained viral clearance in treatment-naive patients (RR = 0.72; 95% CI = 0.68, 0.76), relapsers (RR = 0.63; 95% CI = 0.54, 0.73), and non-responders (RR = 0.89; 95% CI = 0.84, 0.94) [27]. This gave the following numbers needed to treat for beneficial effects (NNT_B): for reduction in mortality/morbidity 444 (95% CI = 302, 5650); for clearing of HCV-RNA 4 (4, 5); and for improving the histological response 8 (17, 100).

This analysis also gave information about the increased toxicity of adding ribavirin, with the following numbers needed to treat for one harm to occur (NNT_H): anemia 4 (4, 5); leukopenia 4 (3, 7); rash 11 (9, 17); pruritus 13 (10, 20); insomnia 14 (6, 20); dermatitis 14 (8, 50); dyspnea 17 (11, 25); fatigue/weakness 17 (11, 33); dry skin 20 (11, 50); anorexia/nausea 20 (13, 50); dyspepsia 20 (13, 50); pharyngitis 20 (13, 100); cough 20 (14, 33). There were also values of NNT_H for dosage reductions 14 (11, 17) and stopping treatment 50 (33, 100).

Treatment with peginterferon alfa-2b + ribavirin can achieve a complete clinical response in about 75% of patients with hepatitis C-related vasculitis. A complete clinical response correlates with the eradication of the virus and requires a shorter treatment period than that previously reported for interferon alfa plus ribavirin (14 months) [28]. The short course was well tolerated, although one patient withdrew because of neutopenia [29].

ORGANS AND SYSTEMS

Respiratory

Cough occurs more commonly in patients taking a combination of interferon + ribavirin compared with interferon alone. In four patients who developed a chronic cough while taking peginterferon + ribavirin for chronic hepatitis C infection a capsaicin cough challenge test showed that cough reflex sensitivity was significantly increased during treatment; the cough resolved within 2–6 weeks after withdrawal and reflex sensitivity improved [30].

In a prospective study of spirometry at 0, 2, and 12 weeks in 31 patients taking ribavirin + peginterferon for chronic hepatitis C, 19 reported dyspnea, but there were no associated changes in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), or the ratio of FEV_1/FVC [31].

A 50-year-old man developed progressive dyspnea over 4 months, progressing to a cough followed by frequent and abundant elimination of bronchial casts. The symptoms resolved 30 days after withdrawal and no other causes were found [32].

A 53-year-old man with chronic hepatitis C was given peginterferon alfa-2a + ribavirin and after 12 weeks developed dyspnea on extreme exertion, with episodes of coughing followed by voluminous expectoration consisting of large pieces (up to 8.0 cm in length) of mucus-like material mimicking bronchial casts [33]. He was given prednisone and partially improved. Later, when peginterferon + ribavirin was withdrawn, the respiratory complaints completely resolved.

In a systematic review of case reports of pneumonitis in patients receiving peginterferon and ribavirin for chronic hepatitis C infection, 58 cases were traced [13]. Pneumonitis presented with any of the combination of fever, dyspnea, and cough and was fatal in 7% of cases, exclusively with peginterferon alfa-2b.

Nervous system

Headache is a frequent adverse reaction to combination therapy with ribavirin + interferon. However, headaches have not been reported in early controlled trials of ribavirin monotherapy for chronic hepatitis C, and the frequency of this adverse reaction is comparable in patients treated with interferon and ribavirin and in interferon monotherapy. Of 452 patients treated with combination therapy for chronic hepatitis C, seven developed new severe migraine headaches and two had worsening of pre-existing migraine [34]. The symptoms mostly started with a delay of several weeks to months. In seven patients, the migraine improved considerably or resolved when ribavirin was withheld or the dose was reduced. All of them had a recurrence when they were re-challenged with full-dose ribavirin. A causal link between ribavirin and migraine appears plausible, but has not been proven.

Progressive multifocal leukoencephalopathy in an HIV negative patient has been attributed to pegylated interferon alfa-2a + ribavirin [35].

A 64-year-old man developed parkinsonism while taking peginterferon alfa-2a and ribavirin for chronic hepatitis C and did not improve when the drugs were withdrawn; he responded to co-beneldopa [36]. This may have been coincidental.

A 29-year-old man with chronic hepatitis C related to intravenous drug use developed a unilateral facial nerve palsy after taking ribavirin 800 mg/day + peginterferon for 2 weeks [37]. The facial weakness persisted during 24 weeks of therapy and resolved 4 weeks after completing treatment.

In a retrospective analysis of the WIN-R trial, a randomized, controlled comparison of fixed versus weight-based ribavirin doses, eight of 4913 patients developed *seizures* during therapy [38]. Three had a generalized

tonic–clonic seizure and the seizure type was unknown in five. One patient had taken long-term antiepileptic drugs before therapy and one started therapy for seizure recurrence. None had recurrent seizures after completion of treatment.

Sensory systems

Vision

Retinal vein thrombosis has been associated with peginterferon alfa 2b + ribavirin in a 46-year-old man with chronic hepatitis C [39].

Visual complications were prospectively analysed in 84 patients taking ribavirin + peginterferon alfa for chronic hepatitis C [40].

Retinopathy was reported in 22 patients, with retinal hemorrhages and significant visual impairment in eight and four patients respectively. Withdrawal of therapy in six patients did not result in resolution. Two Spanish patients developed transient visual disturbances due to retinopathy during treatment with ribavirin and peginterferon alfa [41]. In one case the symptoms resolved spontaneously despite continuation of treatment and in the other the symptoms resolved after withdrawal. Permanent visual loss due to retinopathy also occurred in a 65-year-old man who took ribavirin + peginterferon alfa for 12 weeks; there were multiple cotton-wool spots bilaterally and visual acuity failed to improve 4 months after withdrawal [42].

A 62-year-old man who took ribavirin + peginterferon alfa for chronic hepatitis C developed branch retinal artery and central retinal vein occlusion [43].

Acute bilateral retinal detachment occurred in two patients taking ribavirin + peginterferon alfa; withdrawal of both agents and high-dose glucocorticoids only led to partial improvement in one case [44]. Inflammatory retinal detachment (Vogt–Koyanagi–Harada disease) occurred in a 58-year-old woman with concomitant hypertension who took ribavirin 400 mg + weekly interferon; her visual symptoms improved only partly on withdrawal of both drugs following high-dose oral glucocorticoids [45].

A 38-year-old man developed ischemic optic neuropathy after taking ribavirin 800 mg/day + peginterferon alfa for 6 months; his visual acuity and field defect failed to improve despite withdrawal of interferon and therapy with high dose systemic steroids [46].

It is a notable feature of most of these reports that the visual defects did not resolve or resolved only partly after withdrawal. This suggests that either the drugs were causative and the effects were irreversible (as may have been the case in retinal detachment) or that the effects were coincidental and not due to the drugs at all.

- A 53-year-old black man with a history of substance abuse developed chronic hepatitis C and was given interferon and ribavirin [47]. After 4 month he developed bilateral cotton wool spots and retinal hemorrhages in the left eye. The retinopathy persisted for several months but resolved in both eyes before the treatment was withdrawn. He had no visual complaints or changes in visual acuity.

It is not clear that the drugs were responsible for the adverse reaction in this case.

Auditory function

Sensorineural hearing loss has been attributed to interferon plus ribavirin [48].

- A 57-year-old man developed vertigo, tinnitus, bilateral hearing loss and postural intolerance temporally related to the administration of pegylated interferon alfa-2b + ribavirin for chronic hepatitis C viral infection. He had bilateral high-frequency sensorineural hearing loss, vertigo with saccadic intrusions during fixation and smooth visual pursuit, supine hypertension and orthostatic hypotension with inadequate reflex compensatory cardiovascular responses, and a hemolytic anemia. Audiometry showed changes that suggested damage to the cochlear outer hair cells. Withdrawal of therapy resulted in rapid clinical resolution with mild residual hearing loss and tinnitus.

Transient sensorineural hearing loss has been described in two patients with chronic hepatitis C who took ribavirin + peginterferon alfa [49]. A 65-year-old man developed unilateral sensorineural hearing loss during therapy with ribavirin + interferon for 28 weeks; despite withdrawal of both agents there was no recovery after 12 months [50]. The fact that the hearing loss was unilateral and did not resolve after drug withdrawal suggests that it was not drug-related.

Other similar cases have been reported, albeit in some cases with unilateral effects [51,52], which suggests that the drugs may not have been responsible.

Taste

In 19 patients with chronic hepatitis C genotype 1 infection, all of whom were given peginterferon alfa-2b + ribavirin, sensitivity to salt and sweet tastes was impaired after 12 weeks and bitter tastes were described as being more unpleasant than before; appetite was also impaired [53].

Psychological

Cognitive dysfunction has been studied in 47 patients with chronic hepatitis C during treatment with peginterferon alfa + ribavirin for 48 weeks in standard doses; cognitive performance was significantly impaired after 12 weeks compared with controls [54].

In 26 patients with chronic hepatitis C taking peginterferon alfa-2a or alfa-2b and ribavirin all aspects of attention were impaired after 12 weeks and the dysfunction did not resolve 8 weeks after withdrawal [55]. The authors hypothesized that there may have been irreversible damage to the dorsolateral prefrontal cortex or anterior cingulate cortex.

Psychiatric

In a prospective study of 79 patients who were hepatitis C-positive and took long-term ribavirin + peginterferon alfa, with or without escitalopram, there were psychiatric symptoms (low mood, anxiety, impaired concentration, hostility, and depression) in 19, 15, 26, 17, and 14 patients respectively without escitalopram. [56]. There were lower incidences in those who took concomitant antidepressants.

In a prospective study of depressive symptoms in 129 patients taking ribavirin + peginterferon alfa there was a rise in the average Beck Depression Inventory score, particularly in patients with subclinical depressive symptoms before treatment [57].

- A 48-year-old man developed severe depression with suicidal ideation after taking ribavirin 1000 mg/day + interferon for 3 months; he failed to improve despite antidepressant therapy but his symptoms improved after withdrawal of both agents [58].

Of 100 patients taking peginterferon + ribavirin for hepatitis C infection (37 men and 63 women), 39 fulfilled the diagnostic criteria of DSM-IV for major depression, which was more common in the women [59]. Somatic symptoms were common, including myalgias, headache, joint pain, nausea/vomiting, abdominal pain, and bouts of palpitation.

Endocrine

Thyroid

Of 107 patients with non-cirrhotic chronic hepatitis C, who were given interferon plus ribavirin for 24 weeks, 20 developed thyroid dysfunction compared with 60 controls awaiting treatment [60]. Women were at a higher risk (RR = 11). Hypothyroidism was more common than hyperthyroidism.

In a retrospective study of 260 patients who received interferon + ribavirin for hepatitis C infection 10% developed a suppressed serum TSH (0.8% Graves' disease, 9.6% transient thyroiditis) and 12% developed a raised serum TSH; 1.5% developed permanently hypothyroidism and requiring levothyroxine [61]. Women had a relative risk of thyroid dysfunction of 1.96 (95% CI = 1.8, 3.0). A serum TSH of 1.75 mU/l or more and a positive thyroid peroxidase antibody titer before therapy were associated with relative risks of 6.0 (95% CI = 3.0, 13) and 4.4 (95% CI = 2.6, 6.5) respectively. The combination of baseline TSH and thyroid peroxidase antibody data predicted progression to thyroid dysfunction with a sensitivity of 95%.

A 62-year-old woman with chronic hepatitis C developed *Hashimoto's thyrotoxicosis* followed by type 1 diabetes mellitus after the addition of ribavirin 600 mg/day to long-term peginterferon alfa [62]. She continued to take both agents, but required long-term insulin and thyroxine replacement.

Of 26 patients taking ribavirin + peginterferon alfa 12 developed autoimmune or non-autoimmune thyroiditis [63]. Levothyroxine replacement was required in all cases.

In a prospective investigation of the incidence of thyroid disorders in patients with chronic hepatitis C before and during treatment with ribavirin + peginterferon thyroid function was studied in 65 anti-HCV and viral RNA-positive patients [64]. In 11 patients thyroid dysfunction occurred within the first 12 weeks, and 18 developed thyroid disorders by 24 weeks, seven with thyroid dysfunction and 11 with antithyroid peroxidase antibodies.

Polyglandular disorders

Type 1 diabetes mellitus and thyroid disease reportedly develop in 0.08–2.6% and 10–15% of patients treated with combined interferon-alfa + ribavirin for chronic hepatitis C, but rarely coexist; however, both conditions have been reported in a 33-year-old woman [65]. In another case, a 55-year-old woman developed type 1 diabetes and had a recurrence of Graves' disease during treatment with peginterferon alfa + ribavirin for chronic hepatitis C [66]. There were serum anti-glutamic acid decarboxylase antibodies and the authors suggested that she had autoimmune polyglandular syndrome type III.

Hematologic

Time-dependent and dose-dependent hemolytic anemia (eventually associated with hyperbilirubinemia and a high reticulocyte count) is the only major toxic reaction associated with oral or intravenous ribavirin and is reversible on withdrawal.

A 49-year-old man who took long-term ribavirin + peginterferon alfa for chronic hepatitis C developed an *autoimmune* hemolytic anemia after 56 weeks of therapy and required transfusion and withdrawal of both agents [67].

Of eight children aged 9–14 years with La Crosse encephalitis treated with high-dose intravenous ribavirin (33 mg/kg loading dose, followed by 16 mg/kg 6-hourly for 4 days and then 8 mg/kg 8-hourly for 3 days), four developed a hemolytic anemia necessitating drug withdrawal [68]. Another seven children who received lower doses (25 mg/kg loading dose, followed by 15 mg/kg 8-hourly for 10 days) did not develop hemolytic anemia.

Of 169 adults treated with ribavirin + interferon, 93 (40%) developed symptomatic anemia during the first 12–18 weeks of treatment; 76 of them were given erythropoietin and 68 required dosage reduction or withdrawal of therapy [69].

Pure red cell aplasia can also be associated with ribavirin and pegylated interferon alfa as well as with hepatitis A, B, or C infections. Anemia due to pure red cell aplasia was reported in a 69-year-old man who took ribavirin 800 mg/day + peginterferon [70]. Ribavirin-associated pure red cell aplasia is fully reversible after withdrawal [71].

A 30-year-old man with chronic hepatitis C infection developed activated protein C resistance, increased factor VIII activity, a raised fibrinogen concentration, and hyperhomocysteinemia after taking peginterferon alfa + ribavirin for 6 months, when he had a pulmonary embolism [72]. The hematological abnormalities returned to normal 3–6 months after drug withdrawal.

Incidence

In patients taking ribavirin plus interferon alfa-2b the average fall in hemoglobin is 2–3 g/dl. Of 57 patients taking ribavirin 800 mg/day 28 were randomized to a high dose of peginterferon alfa-2b once a week (3 micrograms/kg for 1 week, 1.5 micrograms/kg for 3 weeks, and 1.0 microgram/kg for 44 weeks) and 27 patients were randomized to receive a low dose (0.5 micrograms/kg) for 48 weeks; three patients required reduced doses of ribavirin because of anemia [73].

In 140 patients with Nipah virus infection there was no difference in the incidence of adverse reactions between those who elected to have ribavirin treatment and those who refused [74]. Dosing was based on recommendations used to achieve the same approximate concentrations as those seen with 100–1200 mg/day in the treatment of hepatitis C. Anemia occurred in 37% of the ribavirin-treated patients and in the same number of controls.

In 321 patients receiving peginterferon alfa + ribavirin, mean platelet count at baseline was 207×10^9/l in non-cirrhotic patients (n = 253) and 132×10^9/l in those with cirrhosis (n = 68) [75]. The mean fall in platelet count during treatment was 42% (from 191 to 113×10^9/l) and there was severe thrombocytopenia (platelet counts below 50×10^9/l) in 30 patients; nine developed platelet counts below 25×10^9/l. The were 48 instances of bleeding in 27 patients, only one of which, due to gastrointestinal angiodysplasia, was severe in a patient without severe thrombocytopenia at the time. Minor bleeding was more common when platelet counts were below 50×10^9/l.

Mechanisms

The anemia associated with peginterferon + ribavirin is thought to be a mixed form of ribavirin-induced hemolysis and interferon-induced myelosuppression. However in an 8-week study of 97 patients receiving peginterferon + ribavirin, while the mean hemoglobin fell significantly from 14.4 to 11.9 g/dl the serum erythropoietin responses were lower than seen in historical controls with iron deficiency [76]. The mean dosage of ribavirin was reduced from 986 to 913 mg/day. Only 74% maintained their dosage of ribavirin.

Detailed studies of the effects of ribavirin on erythrocyte ATP content and on the hexose monophosphate shunt have been conducted in vitro. ATP concentrations were significantly reduced and the hexose monophosphate shunt increased, suggesting erythrocyte susceptibility to oxidation. In vivo, ribavirin, alone or in combination with interferon, was associated with significant reductions in hemoglobin concentrations and a marked increase in absolute reticulocyte counts. Erythrocyte Na/K pump activity was significantly reduced, whereas K/Cl co-transport and its dithiothreitol-sensitive fraction and malondialdehyde and methemoglobin concentrations increased significantly. Ribavirin-treated patients showed an increase in aggregated band 3, which was associated with significantly increased binding of autologous antibodies and complement C3 fragments, suggesting erythrophagocytic removal by the reticuloendothelial system [77].

Time-course

In a randomized controlled trial of high-dose interferon alfa-2b plus oral ribavirin for 6 or 12 months in 50 patients with chronic hepatitis C, the sequential effects of treatment on hemoglobin, leukocytes, and platelets were recorded [78]. There was a fall in hemoglobin, and the lowest concentrations were recorded after 6 months of treatment in both groups. All hematological measurements returned to normal after the end of treatment.

Susceptibility factors

In a genome-wide association study of patients with chronic hepatitis C, two functional variants in the ITPA gene, which cause inosine triphosphatase (ITPase) deficiency, protected against ribavirin-induced *hemolytic anemia* in 304 patients [79]. The polymorphisms rs1127354 and rs7270101 were associated with a reduction in hemoglobin and the minor alleles of each variant were protective.

In a genome-wide study in 923 Japanese patients with hepatitis C virus 1b infection treated with peginterferon + ribavirin, a variant located upstream of the inosine triphosphate pyrophosphatase gene on chromosome 20p13 was significantly associated with treatment-induced anemia [80]. Several SNPs were strongly associated with the fall in hemoglobin, including the non-synonymous SNP rs1127354. Another SNP, the splicing variant-related rs7270101, was not polymorphic in the Japanese population. Stratified analysis based on the rs1127354 genotype showed that inosine triphosphate pyrophosphatase expression does not correlate with the fall in hemoglobin, suggesting that rs1127354 is a direct causal variant in the Japanese population.

Factors that could help predict hematological abnormalities in patients with chronic hepatitis C taking pegylated interferon and ribavirin have been studied in 136 patients over 4 years, of whom 52 developed neutropenia (n = 28), anemia (n = 30), or thrombocytopenia (n = 11). Genotype 1, a history of hypertension, a low baseline platelet count, a low baseline hemoglobin, and a raised serum creatinine concentration were significant factors [81].

A low pretreatment platelet count, the dose of interferon alfa, and the haptoglobin phenotype are susceptibility factors for ribavirin-induced anemia, and the fall in hemoglobin is independent of dose in the therapeutic range [82]. In five patients with chronic hepatitis C on hemodialysis who received subcutaneous interferon alfa-2b and oral ribavirin for 40 weeks, the dose of ribavirin was titrated based on hemoglobin, with bone marrow support by erythropoietin [83]. There was significant bone marrow toxicity in all five. A dose of 200 mg/day produced a steady-state AUC comparable to that obtained with 1000–1200 mg/day in historical controls with normal renal function. More severe anemia was possibly due to chronic renal insufficiency in addition to the prolonged effects of ribavirin.

Management

Treatment of ribavirin-induced hemolytic anemia with recombinant human erythropoietin has been described in 13 patients [84]. The hemoglobin concentration increased from a nadir of 10.2 g/dl to a median of 11.5 g/dl and ribavirin treatment did not have to be withdrawn.

Mouth

Tongue hyperpigmentation has been described during therapy with ribavirin + peginterferon alfa in chronic hepatitis C [85]. Hyperpigmentation of the oral mucosa and

tongue has been reported in a 40-year-old Caucasian woman with hepatitis C infection who had taken peginterferon alfa-2a 90–180 micrograms/week plus ribavirin 1 g/day for 12 weeks; she had tongue discomfort and noticed irregular black patches on the lateral surface of the tongue and oral mucosa [86].

A 54-year-old woman developed numerous asymptomatic dark brown macules on her tongue and oral mucosa after taking peginterferon alfa-2a and ribavirin for 4 months [87].

A 66-year-old woman developed dark brown, asymptomatic pigmentation on the dorsum of the tongue after taking peginterferon alfa plus ribavirin for 32 weeks; her lesions resolved within 6 months after withdrawal [88].

A 36-year-old woman developed lingual hyperpigmentation while taking ribavirin + pegylated interferon for hepatitis C virus infection [89]. She had dark gray macules on the bilateral dorsolateral surfaces of her tongue, but no oral erosions or any other nail or cutaneous abnormalities. The only new medications that she had begun in close temporal proximity to the onset of the discomfort were peginterferon alfa-2b and ribavirin, both of which she had taken for 4 months.

Gastrointestinal

A man with hepatitis C took ribavirin + peginterferon alfa and developed malabsorption [90]. Histological and serological investigations confirmed *celiac disease*. The symptoms improved following a strict gluten-free diet and withdrawal of both agents.

A 53-year-old woman with hepatitis C infection was given peginterferon 180 micrograms/week and ribavirin 1.2 g/day. After 12 weeks she developed a neutropenia of 550×10^6/l and a secondary enterocolitis, with bowel wall thickening involving the cecum and proximal ascending colon; she responded to broad-spectrum antibiotics, supportive treatment, and G-CSF (filgastrim) [91].

Liver

Liver damage has been attributed to ribavirin + interferon.

- A 38-year-old woman with stable chronic hepatitis C developed *fulminant hepatitis* while taking ribavirin + peginterferon alfa [92]. Jaundice and clotting deteriorated despite withdrawal of interferon and the use of high-dose glucocorticoids, and she required liver transplantation.
- A 62-year-old woman with chronic hepatitis C took ribavirin + interferon for 72 weeks and developed persistently abnormal biochemistry (raised aminotransferases, alkaline phosphatase, and gamma-glutamyl transferase) despite remaining seronegative for hepatitis C virus [93]. A liver biopsy showed *cirrhosis*, which was attributed to the antiviral drug therapy.

As part of a multicenter, randomized, double-blind, placebo-controlled trial of ribavirin in 59 patients with hepatitis C virus infection, liver biopsies were studied for iron deposition [94]. Increased total iron deposition, preferentially in hepatocytes, occurred during a 9-month course of ribavirin. The deposition had no apparent effect on the biochemical or histological response to ribavirin therapy.

Urinary tract

Ribavirin can cause hemoglobinuria, resulting in black urine [95].

Hair

Irreversible alopecia has been associated with ribavirin + peg-interferon [96].

Skin

The addition of ribavirin to interferon therapy may be associated with an increased risk of adverse skin reactions [97]. The adverse cutaneous events that can occur in patients taking interferon plus ribavirin have been reviewed [98].

Photosensitivity after administration of ribavirin has been described [34]. A well-documented photoallergic reaction in a woman who was taking both ribavirin and interferon alfa provided evidence that ribavirin is a potential photosensitizer for UVB, a problem that may become increasingly relevant in patients with chronic hepatitis C taking combination therapy for 6–12 months with interferon alfa and ribavirin [99].

Occasional rashes in areas of drug contact and conjunctival irritation occurred when aerosolized ribavirin was used for 10 months in an infant with immunodeficiency [100].

Pruritus, xerosis, and mild skin eruptions, such as eczema and lichen planus, are common (23%) during ribavirin plus interferon therapy [101]. In three cases oral lichen planus worsened during treatment of chronic hepatitis C with pegylated interferon and ribavirin [102], and a 58-year-old woman developed a lichenoid eruption on the hands after taking interferon alfa-2b and ribavirin for 6 days; the lesions resolved within 1 week after withdrawal [103]. Control of these symptoms mostly requires sustained therapy with moderately potent to potent topical glucocorticoids, combined with baseline emollients throughout the combination treatment period. However, there are occasional reports of marked erythematous maculopapular eruptions starting 3–4 days after the start of combination therapy [104]. Although this form of skin reaction (which is probably T cell mediated) is rare, it should be emphasized that it can occur early during treatment and can evolve into Stevens–Johnson syndrome.

Dermatitis occurred in 36 patients who were given ribavirin + pegylated interferon [105]. Half of the patients had clinical symptoms within the first month of combination treatment, and the first signs typically appeared distant from the sites of peginterferon injection. All complained of generalized itch, and most had xerosis and erythematopapulo-microvesicular lesions with a predilection for the extensor surfaces of the limbs and skin sites exposed to friction. Seven had skin biopsies with a superficial dermal perivascular inflammation with spongiosis and parakeratosis; erythrocyte extravasation, sparse keratinocyte necrosis, and extension of the inflammation to the interface were variable; the last of these occurred in the clinically more severe cases. Two patients developed specific

skin signs that differed from the eczema-like pattern described above. One patient with generalized eczematous skin changes eventually developed malar hypertrichosis lanuginosa and bullous skin lesions with milia on the backs of both hands, leading to a diagnosis of porphyria cutanea tarda; one patient developed a bullous eruption with histological features of acantholytic dermatitis with a non-specific immunohistological profile.

Five cases of Meyerson's syndrome (halo dermatitis), a benign eczematous rash around a pre-existing nevus, have been reported during treatment for hepatitis C [106,107]. This syndrome has been reported with interferon-alfa-2b but not ribavirin in other conditions and resolved on withdrawal of therapy.

There is a well-established association between hepatitis C virus infection and porphyria cutanea tarda. However it is thought that ribavirin increases the risk by increasing iron overload via hemolysis. Two cases of porphyria cutanea tarda have been reported after treatment with ribavirin and interferon [108].

There have been reports of cutaneous sarcoidosis associated with pegylated interferon alfa plus ribavirin treatment [109]. Sarcoid granulomata have been attributed to ribavirin + peginterferon alfa.

- A 56-year-old woman who took ribavirin + peginterferon alfa for 3 months developed sarcoid granulomas at the site of previous insertion of a facial cosmetic filler [110]. The lesions regressed after 6 months after withdrawal of both agents.
- A 55-year-old man who took ribavirin + interferon alfa for 48 weeks developed widespread subcutaneous nodules on the legs, elbows, and groin 1 month after completing therapy [111]. A skin biopsy showed epithelioid granulomas consistent with sarcoidosis. A CT scan showed paratracheal, subcarinal and hilar adenopathy and serum ACE and calcium were elevated. The symptoms and radiographic evidence of sarcoidosis resolved over 3 years without treatment.

Musculoskeletal

A 48-year-old man developed rheumatoid arthritis 2 months after completing a 6-month course of ribavirin + peginterferon for chronic hepatitis C [112]. There was symmetrical erosive polyarthritis in the wrist and the metacarpophalangeal joints, which required long-term treatment with methotrexate and sulfasalazine.

Sexual function

In a 37-year-old man taking ribavirin and pegylated interferon for hepatitis C, the percentage of progressive spermatozoa and the number of motile sperm per ejaculate fell during treatment [113]. The round cell/spermatozoa ratio, a measure of *abnormal spermatogenesis*, rose from 2.6% to 24% and returned to baseline 4 months later. The sperm DNA fragmentation index increased markedly during treatment from 15% to 69% at 7 months and was still raised 8 months later.

Reproductive system

In 15 men with chronic hepatitis C infection receiving peginterferon alfa-2a + ribavirin, ribavirin concentrations were higher in seminal fluid than in serum. Abnormalities of spermatozoa (asthenoteratozoospermia: n = 6; asthenozoospermia: n = 3; teratozoospermia: n = 3) were common at baseline, and sperm density, percentage motility, and the percentage of sperm with normal morphology fell during antiviral therapy [114].

Immunologic

Vogt–Koyanagi–Harada disease, a disease of melanocyte-containing organs, characterized by uveitis, poliosis, vitiligo, and meningitis, also known as uveodermatologic syndrome, thought to be due to T helper cell-mediated autoimmunity, has been associated with interferon alfa + ribavirin in two men with chronic hepatitis C infection [115,116].

Infection risk

The susceptibility factors for bacterial infections have been studied in patients co-infected with HIV and hepatitis C virus taking pegylated interferon with or without ribavirin [117]. There were 18 bacterial infections in 17 of the 383 patients who received at least one dose of study medication. There were two cases of pyelonephritis and one case of prostatitis (*Escherichia coli*), one case of diarrhea (*Klebsiella oxytoca*), two of septicemia (one due to *Salmonella enterica* and one to *Staphylococcus aureus*), one case of *Streptococcus pneumoniae* meningitis, eight lower respiratory tract infections (two in the same patient), one case of sinusitis, and two cases of cellulitis. Factors that were independently associated with the risk of bacterial infection were related to the duration of hepatitis C infection and to markers of liver fibrosis but not to neutropenia or characteristics of the HIV infection, including CD4 cell count.

- A 35-year-old man, who had had a splenectomy at age 14 years but had not been immunized against *Streptococcus pneumoniae*, developed pneumococcal meningitis while taking interferon and ribavirin for chronic hepatitis C [118].

A similar case has been reported in a 61-year-old woman, with a fatal outcome [119].

SECOND-GENERATION EFFECTS

Pregnancy

Ribavirin is a category X product in the US FDA's classification and is contraindicated in women who are or may become pregnant [120]. It is also contraindicated in men whose partners may become pregnant. The US Ribavirin Pregnancy Registry is a surveillance system for exposure to ribavirin during pregnancy or within 6 months after treatment is stopped; it relies on patients and health-care providers to provide voluntary outcome data [121].

Teratogenicity

Ribavirin is teratogenic and embryotoxic in laboratory animals and should not be given to pregnant women.

Concern has been expressed about the safety of people in the same room as patients being treated with ribavirin by aerosol, particularly women of child-bearing age. However, no ribavirin was detected in the urine, plasma, or erythrocytes of 19 nurses exposed to ribavirin administered via ventilator, oxygen tent, or oxygen hood over 3 days [122].

The voluntary Ribavirin Pregnancy Registry was established in 2003 to monitor pregnancy exposures to ribavirin and to evaluate the potential human teratogenicity of prenatal exposure [123]. It documents pregnant women who have been exposed to ribavirin during pregnancy or during the 6 months before conception either directly (by taking ribavirin) or indirectly (through sexual contact with a man taking ribavirin). After more than five years, 49 live births after direct exposure and 69 live births after indirect exposure have been documented, including six cases of birth defects (three direct exposures and three indirect), all among live-born infants: two cases of torticollis and one each of hypospadias; polydactyly and a neonatal tooth; glucose-6-phosphate dehydrogenase deficiency; ventricular septal defect and cyst of the fourth ventricle of the brain.

SUSCEPTIBILITY FACTORS

Genetic

In a study of single-nucleotide-polymorphisms in 1002 adults taking ribavirin + peginterferon, there was a rapid fall in hemoglobin concentrations during the initial 4 weeks of treatment in patients with the rs1127354 genotype CC in the inosine triphosphate pyrophosphatase (ITPA) gene [124]. Hemoglobin concentrations in genotype CC patients stabilized by week 8 and did not fall further. Similarly, in 61 patients taking telaprevir and ribavirin + interferon [125]. The fall in hemoglobin was highest in those with genotype CC in the ITPA gene at weeks 2, 4, and 12, although outcomes after the end of treatment were not recorded.

Renal impairment

The clearance of ribavirin is impaired in patients with renal dysfunction, and it is not removed by hemodialysis. It is therefore not recommended for patients with a creatinine clearance under 50 ml/minute. However hepatitis C infection is associated with renal complications, such as membranoproliferative glomerulonephritis with or without cryoglobulinemia, membranous glomerulonephritis, and focal segmental glomerulosclerosis. Of seven patients treated with interferon six became HCV-RNA PCR negative, four maintained both virological and renal remission, and one maintained virological and partial renal remission [126]. Ribavirin-induced anemia was managed in five patients with low-dose iron and erythropoietin. The authors concluded that ribavirin can be used, with reasonable safety, in HCV-related vasculitis and glomerulonephritis irrespective of renal function.

Transient acantholytic dermatosis (Grover's disease) was first described by Grover in 1970 as a pruritic, self-limiting, popular, or papulovesicular eruption, mainly distributed on the trunk of white middle-aged men. The histopathological hallmark is suprabasal acantholysis at different levels of the epidermis. Its origin is uncertain; most cases are related to sunlight, heat, or sweating. Grover's disease has been attributed to ribavirin [127].

- A 55-year-old man with chronic hepatitis C presented with a pruritic papular eruption on the trunk lasting 2 weeks. He had multiple, erythematous, excoriated papules on the neck, trunk, upper arms, and thighs. The lesions appeared 2 weeks after combination therapy with oral ribavirin and subcutaneous interferon alfa-2b. He had previously been treated with interferon alfa alone (in the same dosage). On withdrawal of ribavirin the lesions gradually faded, but they returned 1 week after reintroduction.

DRUG–DRUG INTERACTIONS

See also Zidovudine

General

The intracellular triphosphorylation and pharmacokinetics of lamivudine, stavudine, and zidovudine have been assessed in 56 patients co-infected with human immunodeficiency virus and hepatitis C virus receiving peginterferon alfa-2a 180 micrograms/week plus either placebo or ribavirin 800 mg/day; there was no difference [128].

Azathioprine

In a retrospective review of the medical records of eight patients who developed severe pancytopenia after administration of azathioprine, interferon alfa, and ribavirin, bone marrow suppression reached a nadir after a mean interval of 4. 6 weeks, at which time the mean platelet count was 70×10^9/l, the mean hemoglobin 7. 8 g/dl, and the mean neutrophil count 450×10^6/l [129]. All had a normal thiopurine methyltransferase genotype. In two patients in whom azathioprine metabolites were measured, myelotoxicity was accompanied by raised total methylated metabolite concentrations and reduced 6-tioguanine nucleotide concentrations. Pegylated interferon alfa and ribavirin were withdrawn and the full blood count returned to normal. There was no recurrence when peginterferon was reintroduced with ribavirin or azathioprine alone. The authors concluded that the combination of inosine monophosphate dehydrogenase inhibitors with purine analogues should be avoided. Another similar case has been reported [130].

Coumarin anticoagulants

An interaction of warfarin with ribavirin has been reported [131].

- In a 61-year-old white man with chronic hepatitis C, who took interferon plus ribavirin, the dosage of warfarin had to be increased by about 40% (from 45 to 63 mg/week) in order to

maintain the desired degree of anticoagulation. This effect was reproduced on rechallenge with ribavirin.

The mechanism of this supposed interaction is not known. For example, ribavirin is cleared by intracellular phosphorylation and its metabolites by the kidneys, warfarin by CYP isoenzymes in the liver; warfarin is highly protein bound, ribavirin is not. However, an effect on warfarin absorption or its action on clotting factor synthesis is possible.

Didanosine

Multisystem organ dysfunction and lactic acidemia occurred in two of 15 patients with HIV and hepatitis C infections who received interferon alfa, didanosine, and ribavirin [132]. Co-administration of didanosine with ribavirin can lead to increased toxicity secondary to raised intracellular concentrations of phosphorylated didanosine [133,134]. Thus, the evidence suggests that the combination of didanosine plus ribavirin increases the risk of lactic acidosis.

Interferon alfa-2b

In a randomized 48-week study, 107 patients co-infected with human immunodeficiency virus (HIV) and hepatitis C (HCV) were given interferon alfa-2b together with either a full course of ribavirin or placebo for 16 weeks, followed by ribavirin [135]. More than 80% of the patients in both groups also took HAART and 25–28% took zidovudine. Significantly more patients in those who took the full 48-week course of ribavirin had to reduce the dose of ribavirin because of anemia (28% versus 11%). Of those who also took zidovudine, only those who took the full course of ribavirin had to reduce the dose of ribavirin for any reason (67% versus 24%) or for anemia (60% versus 16%). Zidovudine, but no other nucleoside analogue, was associated with a significantly lower hemoglobin concentration (10.1 versus 13.0 g/dl) and a significantly larger fall (-3.64 versus -2.08 g/dl). However, there was no pronounced association between leukopenia or neutropenia and zidovudine. The combination of zidovudine with interferons and ribavirin should be avoided if possible.

INTERFERENCE WITH DIAGNOSTIC TESTS

The Hb_{A1C} concentration was falsely reduced by joint ribavirin and peginterferon alfa-2b therapy in a 59-year-old man with type 2 diabetes mellitus; after treatment was withdrawn the Hb_{A1C} returned to baseline [136].

MANAGEMENT OF ADVERSE DRUG REACTIONS

The management with epoetin alfa and danazol of anemia during therapy with interferon and ribavirin has been reported [137].

- A 50-year-old African–American man with chronic hepatitis C was initially given subcutaneous interferon alfa-2b (3 mU three times/week) and oral ribavirin 1200 mg/day. The pre-treatment hemoglobin was 14.3 g/dl. There was a good therapeutic response, but the hemoglobin fell firstly to 11.2 g/dl and then to 9.4 g/dl by week 42. This prompted a reduction in the dosage of ribavirin to 800 mg/day, and the hemoglobin rose to 11.8 g/dl. The antiviral therapy was withdrawn at week 48 and reintroduced 3 months later for a relapse. He was given subcutaneous peginterferon alfa-2a (180 micrograms/week) and oral ribavirin 1200 mg/day plus subcutaneous epoetin alfa 4000 U/week to prevent anemia and therefore the need to reduce the dose of ribavirin. Serum hemoglobin at the start of the second course of therapy was 14.7 g/dl and it remained stable throughout the first 12 weeks of therapy. However, at week 16, there was an abrupt fall in hemoglobin from 14.6 to 8.5 g/dl. The ribavirin was immediately withdrawn, the dosage of peginterferon was reduced, and the dosage of epoetin alfa was increased to 60000 U/week. At week 18, the hemoglobin fell to 7.2 g/dl and the peginterferon was withdrawn. At week 20, the hemoglobin reached a nadir of 5.6 g/dl, requiring transfusion with three units of packed erythrocytes. The patient continued to require about one unit of blood every week despite continuing epoetin alfa, which was finally stopped at week 26. Erythropoietin antibodies became detectable by week 12 and peaked at week 24. Danazol 200 mg bd then 400 mg bd was started 8 weeks after the withdrawal of epoetin alfa. The hemoglobin then became stable at 9–10 g/dl for 24 weeks.

MONITORING DRUG THERAPY

In a systematic review of the use of plasma ribavirin concentrations to monitor therapy in patients with chronic hepatitis C (30 studies), a previously published nine-step decision-making algorithm was used to help determine whether measurement is warranted [138]. Some studies have supported and others have refuted the usefulness of ribavirin measurement; most had methodological limitations, such as small sample size, retrospective analyses, and lack of P value adjustment for multiple analyses.

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