

Chapter 15: Management of adverse events and drug interactions of interferon-based therapy for chronic hepatitis C

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Introduction

Good adherence is a key factor for success in the treatment of hepatitis C. However, almost all patients on treatment with interferon plus ribavirin will experience side effects that can threaten good adherence. Therefore, proactive management of adverse events is crucial to avoid suboptimal therapy (missing doses, etc) and treatment discontinuations.

The most common clinical adverse events in patients on treatment with pegylated interferon plus ribavirin are flu-like symptoms, myalgia, sleep disturbances, asthenia, gastrointestinal disorders and depressive mood changes (Table 1).

Psychiatric side effects	Incidence
Fatigue	70-80%
Sleep disturbances	46-65%
Irritability	60-85%
Cognitive disturbances with impairments of concentration and memory	45-60%
Depressive episodes	50-60%
- mild depressive episode	20-40%
- moderate depressive episode	15-30%
- severe depressive episode	1-5%
Delirium, psychosis	1-6%
Suicidal syndrome	<1%

**data from outpatient department, Essen*

Table 1. Incidence of the most reported IFN α induced psychiatric side effects*.

For most adverse events, clinical trials looking at dose moderation have not been done, and because of this, recommendations in this review for management are necessarily partially based on clinical experience.

Flu-like symptoms, fever, arthralgia and myalgia

Flu-like symptoms, fever, arthralgia and myalgia appear a few hours after the injection of pegylated interferon and may last for up to three days. One common approach is the use of paracetamol or other NSAIDs immediately before or after the injection of interferon. Flu-like symptoms usually diminish spontaneously during the first weeks of treatment (Figure 1).

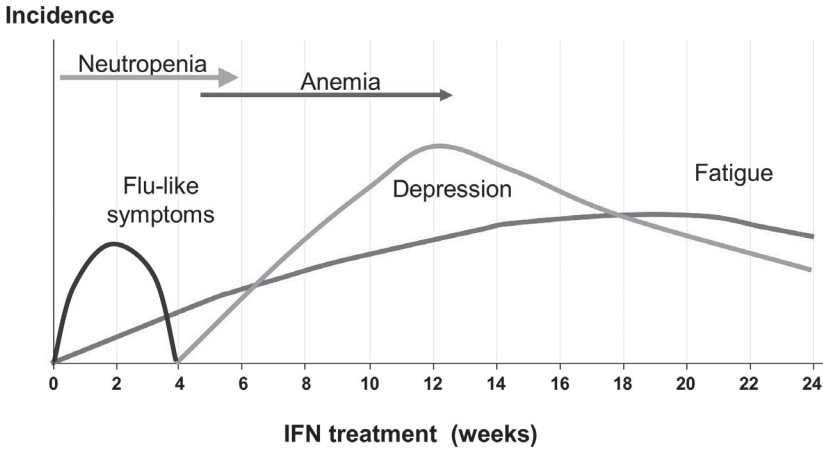


Figure 1. Time course of interferon-associated adverse events.

Low platelets are a contraindication for the use of acetylsalicylic acid, diclofenac or ibuprofen because of the inhibition of platelet aggregation. High doses of paracetamol may result in liver toxicity. Doses exceeding 2 g/day of paracetamol are not recommended.

Gastrointestinal disorders

Nausea can be mitigated by using prokinetic agents such as metoclopramide or domperidone before administering ribavirin. This may also help with the frequently observed loss of appetite.

Dry mouth has been reported as a result of inhibition of saliva production, a frequent complication of ribavirin and may continue post-therapy.

Weight loss

The average weight loss in interferon-based controlled studies is around 6-10% for a treatment period of 48 weeks (Seyam 2004). This may be predominantly due to loss of appetite and reduction in calorie intake. The weight loss is rapidly reversible upon discontinuation of therapy.

Asthenia and fatigue

Asthenia and fatigue are frequent complaints that usually increase slowly in intensity over the first couple weeks of therapy (Figure 1). In patients with marked anaemia these symptoms can be improved by raising low haemoglobin with the use of erythropoietin, a reduction of the ribavirin dosage or red blood cell transfusion (Pockros 2004). Asthenia is also reported by patients without marked anaemia. In these patients hypothyroidism may be the explanation. Symptomatic treatment of asthenia and fatigue in patients without an underlying complication such as anaemia, depression or hypothyroidism is difficult.

Chronic fatigue has been successfully treated in individual cases with antidepressants or tryptophan (Sammot 2002; Schaefer 2008). A first prospective randomised controlled trial showed superior effects of the 5-HT₃ receptor antagonist ondansetron compared to placebo (Piche 2005). However, currently available data does not point to specific treatment recommendations.

Cough and dyspnoea

Cough while on therapy is frequently reported and is most probably due to oedema of the mucosa of the respiratory system. Therefore, advanced, not well-controlled asthma bronchiale may be a contraindication for hepatitis C therapy. Dyspnoea is another frequent complaint with a more complex aetiology involving mucosal swelling, anaemia and asthenia.

Disorders of the thyroid

Hypothyroidism while on interferon-based therapy is reported with an incidence of 3-10% (Bini 2004; Tran 2005). Hyperthyroidism is less frequently observed with an incidence of 1-3% (Bini 2004; Tran 2005). Interferon-induced thyroiditis or the induction of thyroid antibodies is reported as an underlying mechanism. Hypothyroidism is treated via substitution of thyroid hormone whereas clinically symptomatic hyperthyroidism may be treated with β -blockers or carbimazole. Premature termination of interferon-based therapy is usually not necessary. Most cases of hypothyroidism are reversible upon discontinuation of interferon-based therapy, although some cases may need prolonged periods of thyroid hormone replacement therapy.

Psychiatric adverse events

Incidence and profile of psychiatric adverse events

The most commonly emerging IFN α induced psychiatric adverse events are outlined in Table 1. However, data on the frequency of psychiatric side effects differs depending on the design of the trial. Most hepatologic trials are only monitored for “major depression” without using depression scales, leading to an underreporting of mild to moderate depressive episodes. Psychiatric trials use self-rating scales (e.g., SDS-scale, BDI-Scale) or monitor patients via structured interviews utilising the Hamilton Depression Scale (HAMDS) or the Montgomery Asperg Depression Scale (MADRS), rating depressive symptoms and any changes in scores not fulfilling DSM-IV criteria of major depression. With this more sensitive psychiatric rating, over 50% of patients suffer from sleep disorders, chronic fatigue, irritability or cognitive disturbances (Schaefer 2007; Schaefer 2002; Dieperink 2000; Renault 1987). Anxiety occurs in 30-45% especially during the first 2 months of treatment. Mild depression with symptoms like reduced self-esteem, anhedonia, loss of interest, rumination, a diminished libido and spontaneous crying can be observed in 30-60% of the patients. 20-30% of treated patients develop moderate to severe depressive episodes (Bonnaccorso 2002; Dieperink 2000; Renault 1987; Schaefer 2002; Malaguarnera 2002). Suicidal ideation is seen in 5-6% of patients, while suicide attempts have been reported in individual cases (Janssen 1994). Mania has

been reported as a sporadically appearing side effect. Contrary to hitherto existing assumptions, patients with pre-existing psychiatric disturbances do not appear to have a greater risk for development of depression or attempting suicide (Schaefer 2007; Schaefer 2003; Pariante 2002). However, patients with intravenous drug histories seem more likely to discontinue treatment in the first three months compared to controls (Schaefer 2003; Mauss 2004; Schaefer 2007).

Antidepressants frequently used in the hepatitis C study population in recent trials in cases of interferon-associated depression are selective serotonin reuptake inhibitors (SSRIs) such as citalopram, paroxetine or tricyclic antidepressants such as doxepin. The introduction of SSRIs and newer antidepressants has markedly reduced the adverse events profile of antidepressants. Therefore, depending on the major symptoms, current sedating or activating antidepressants, especially SSRIs, are treatment of choice for interferon-induced depressive mood disorders. In patients with predominantly agitation and aggression, other strategies, e.g., modern antipsychotics, may be added.

The efficacy of antidepressants for treatment of interferon α induced depression has been shown in several cohorts (Farah 2002; Gleason 2002; Kraus 2001; Schramm 2000; Hauser 2002; Gleason 2005). Recently, early prospective controlled data shows a significantly better improvement of depressive symptoms after treatment of IFN-associated depression with citalopram (Kraus 2008). SSRIs seem to be the best-suited substances for the treatment of interferon α associated depressive symptoms. However, antidepressants with different receptor profiles (i.e., mirtazapine) and classical antidepressants (i.e., nortriptyline) are also effective (Kraus 2001; Valentine 1995). Nevertheless, tricyclic antidepressants should be used as second choice because of pharmacological interactions and anticholinergic side effects possibly leading to a higher risk of developing delirium, to affect the heart or liver or to interact with other medications. To reduce adverse events and to increase adherence, treatment with antidepressants can be started at a relatively low dose, increasing depending on the effect and tolerability. In general, a therapeutically-relevant antidepressive effect cannot be expected before 8-14 days of treatment. In case of non-response, the dose can be escalated. Treatment adherence should be assessed by monitoring serum levels before patients are switched to a different antidepressant.

Benzodiazepines can be given for a short period in case of severe sleep disturbances, irritability or depression. However, benzodiazepines should be avoided in patients with a history of IV drug or alcohol abuse because of their potential to induce addiction (Schaefer and Mauss 2008).

In case of psychotic symptoms, antipsychotics (e.g., risperidone, olanzapine) can be used at low doses, but patients should be monitored carefully by a psychiatrist. One important risk factor for the development of psychotic symptoms is a history of drug abuse.

Although history of major depression or suicide attempts is considered a contraindication for interferon-based therapy, treatment of patients with pre-existing psychiatric disorders can be initiated in close collaboration with an experienced psychiatrist in a well-controlled setting (Schaefer 2004; Schaefer 2007).

Preemptive therapy with antidepressants

One double-blind randomised study including patients with a malign melanoma demonstrated that 14 days of pre-treatment with 20 mg paroxetine per day reduced the incidence of depression during interferon therapy significantly (Musselmann 2001). Pretreatment with paroxetine also had a positive effect on the development of fears, cognitive impairments and pain during interferon treatment, but not on symptoms such as fatigue, sleep disturbances, anhedonia and irritability (Capuron 2002). A recent prospective controlled trial with HCV-positive people demonstrated that pretreatment with citalopram significantly reduced depression during the first 6 months of antiviral therapy in patients with psychiatric illness compared to controls (Schaefer 2005). Furthermore, prophylactic treatment with SSRIs was also shown to reduce the severity of depressive symptoms in patients who had suffered from severe depression during previous treatment of hepatitis C with interferon α (Kraus 2005). Finally, a recent trial confirmed a protective effect of preemptive initiation of treatment with antidepressants in cases of elevated depression scores before interferon-based therapy is started (Raison 2007). In summary, current data supports the view that all patients with pre-existing depressive symptoms should receive a prophylactic treatment with antidepressants. However, evidence from larger prospective controlled studies are needed in order to answer the question if antidepressants should be given before antiviral plus interferon-based therapy, independent of pre-existing psychiatric disorders.

Sleep disturbances

Patients who have difficulties in falling asleep can be treated with zopiclone or trimipramine. Zolpidem may be used for patients with interrupted or shortened sleep patterns. Although the risk of addiction is markedly reduced compared with other benzodiazepines, only small amounts of zopiclone or zolpidem should be prescribed at a time and therapy should be limited to the period of interferon-based therapy. As sleeping disorders can be a symptom of depression, it is also important to identify existing depressive symptoms and add antidepressants with sedative effects, such as mirtazapine, as needed.

Haematologic and immunologic effects

Interferon-based therapy is accompanied by a marked drop in white blood cells in general, neutrophils and absolute, although not relative, CD4+ cell count. This change in the cellular immune system does not result in an increased number of serious infections even in HIV-coinfected patients (Fried 2002; Manns 2001; Torriani 2004). In general the incidence of serious infections is low (<5%) in patients on interferon-based therapy.

Despite reassuring clinical data, G-CSF is not often used to correct neutropenia. G-CSF has not been proven efficacious in clinical trials for this purpose and its use is off-label.

Haemolytic anaemia induced by ribavirin is further aggravated by the myelosuppressive effect of interferon that inhibits compensatory reticulocytosis (De Franceschi 2000). As a consequence, anaemia (<10 g/dl) is reported in up to 20% of patients (Hadziyannis 2004). In severe cases of anaemia dose reduction of ribavirin is required. In rare cases, red blood cell transfusion may be necessary. Erythropoietin can be successfully used to correct ribavirin-induced anaemia at least partially and to

avoid ribavirin dose reduction or red blood cell transfusions. However, prospective controlled trials have not shown an improved efficacy of hepatitis C therapy in patients who take erythropoietin (Afdahl 2004; Pockros 2004; Shiffman 2007). Erythropoietin is not approved for correction of ribavirin-induced anaemia in hepatitis C therapy.

Mild to moderate thrombocytopenia is frequently observed in patients with advanced liver fibrosis and may complicate interferon-based therapy. Reduction of interferon dosing may be indicated to reverse severe thrombocytopenia. Eltrombopag has been used successfully in studies to increase platelet count in patients with hepatitis C-associated thrombocytopenia (McHutchinson 2007).

Skin disorders and hair loss

Skin disorders such as lichen ruber planus, necrotising vasculitis or porphyrea cutanea tarda are associated with hepatitis C infection. The effects of hepatitis C therapy are often not well-studied and based only on cohort data (Berk 2007).

Interferon plus ribavirin may have an effect on the skin itself including dry skin, itching, eczema and new or exacerbated psoriasis. Ointments with rehydrating components, urea or steroids can be used depending on the nature of the skin disorders. In severe cases a dermatologist should be involved. In particular, eczema and psoriasis may last substantially longer than the treatment period with interferon-based therapy.

Local skin reactions to the injection of pegylated interferon are common and usually present as red indurations lasting days to weeks. Repeated injections at the same site may cause ulcers and should be avoided. Hypersensitivity reactions to pegylated interferons are reported anecdotally.

Hair loss is frequent, usually appearing after the first months of therapy and continuing for some weeks after the cessation of therapy. Alopecia is very rare and hair loss is usually fully reversible, although the structure of the hair may be different after therapy.

Adherence

Adherence data from retrospective analyses suggest that at least 80% of the cumulative dosing of ribavirin and interferon should be taken by patients as a prerequisite for treatment success. Cumulative doses of less than 80% were associated with a steep drop in sustained virologic response (Camma 2005). Another surrogate of adherence is the premature treatment discontinuation rate, which usually ranges from 10–15% with pegylated interferon plus ribavirin (Fried 2002; Manns 2001).

Conclusion

In summary, the toxicity of interferon-based therapy in combination with ribavirin is considerable and requires a deep-seated knowledge and active management, in particular involving psychiatric adverse events.

The first generation of HCV protease and polymerase inhibitors will be combined with interferon and ribavirin as triple combination therapy to improve efficacy of therapy, in particular in HCV genotype 1 patients. Current studies indicate that most agents will have a substantial adverse event profile increasing haematological or dermatological problems while on therapy. Early assessment and therapy of adverse events may prevent premature treatment discontinuation, thereby improving the efficacy of hepatitis C therapy.

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