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Interferon therapy side effects in patients with chronic liver disease attending GIT babylon center

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Abstract
This prospective observational study evaluated the adverse effects of pegylated interferon (PEG-IFN) therapy in 114 patients with chronic hepatitis B (CHB, n=53) and C (CHC, n=61) at the GIT Babylon Center from January 2024 to January 2025. Patients received PEG-IFN alfa-2a (180 µg weekly) and were monitored over three months for side effects, including flu-like symptoms (91.2%), hematological abnormalities (81.5%), and neuropsychiatric issues (34.2%). Laboratory changes, such as reduced hemoglobin (p=0.000) and elevated liver enzymes (p<0.013), were significant, with adverse effects correlating with treatment duration for some symptoms (e.g., arthralgia, p=0.007). Gender and hepatitis type influenced specific side effects, like anemia in CHC patients. These findings underscore the need for vigilant monitoring and supportive care to enhance patient outcomes amidst IFN therapy's challenges, particularly in resource-limited settings where it remains relevant.

Keywords: Chronic hepatitis B, chronic hepatitis C, interferon therapy, adverse effects, patient outcomes.

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are leading causes of chronic liver disease worldwide, contributing significantly to global morbidity and mortality. HBV affects over 2 billion people globally, with an estimated 350-400 million suffering from chronic infection [1]. HCV, on the other hand, infects approximately 170 million people, with 3-4 million new cases reported annually [2]. Both viruses can lead to severe complications such as cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC) [3, 4]. Interferon (IFN)-based therapies, including pegylated interferon (PEG-IFN), have been widely used to treat chronic hepatitis B and C. However, these therapies are associated with significant side effects, which can impact patient adherence and treatment outcomes [5]. This study evaluates the frequency and nature of adverse effects from interferon-based therapy in patients with chronic hepatitis B and C.

HBV infection progresses through four distinct phases: immune-tolerant, immune-active, inactive, and resolution phases. The immune-tolerant phase, common in perinatal infections, is characterized by high viral DNA levels (>10 million IU/mL) and minimal liver inflammation [6]. This phase can last for decades, particularly in individuals infected with HBV genotype C [7]. The immune-active phase involves elevated ALT levels and active liver disease, often leading to HBeAg seroconversion [8]. The inactive phase is marked by low HBV DNA levels (<2,000 IU/mL) and normal ALT, while the resolution phase involves HBsAg clearance, though the risk of HCC remains even after clearance [9, 10].

Treatment is recommended for patients with HBV DNA levels > 200 IU/mL, elevated ALT levels, and significant liver inflammation or fibrosis, as outlined by guidelines from the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and the Asian Pacific Association for the Study of the Liver (APASL) [11, 12]. These guidelines provide varying thresholds for treatment initiation, particularly in cirrhotic patients, who require careful monitoring and early intervention [13].

PEG-IFN has shown efficacy in achieving HBeAg seroconversion and HBsAg clearance in a subset of patients. However, its use is limited by side effects and variable response rates, particularly in genotype D patients [14]. Predictors of response include high ALT levels, low HBV DNA, and favorable genotypes (A, B, and C) [15]. Despite its limitations, PEG-IFN remains a valuable therapeutic option, especially in patients without cirrhosis and those who prefer a finite treatment duration [16].

HCV infection leads to chronic hepatitis in 75-85% of cases, with a significant risk of cirrhosis and HCC over decades [17]. The natural history of HCV is influenced by host factors such as IL28B polymorphisms and viral genotypes, which also play a role in determining treatment response [18].

IFN-based therapies have evolved from standard IFN monotherapy to combination therapy with ribavirin and PEG-IFN, achieving sustained virologic response (SVR) rates of 40-55% [19]. Recent advances in direct-acting antivirals (DAAs) have further improved SVR rates to over 90%, reducing the reliance on IFN-based therapies [20]. However, in resource-limited settings, PEG-IFN combined with ribavirin remains a viable option, despite its association with significant side effects, including flu-like symptoms, hematologic abnormalities, and psychiatric disorders [21]. Extended treatment durations (up to 96 weeks) have shown improved SVR rates in genotype D patients, though this approach is often limited by tolerability issues [22].

Interferons (IFNs) are a group of cytokines that play a critical role in enhancing antiviral defenses by activating immune cells and upregulating major histocompatibility complex (MHC) antigens, thereby improving the immune system's ability to recognize and combat viral infections. They are classified into three main types based on their receptor interactions and functional roles. Type I interferons, such as IFN-α and IFN-β, are primarily used in the treatment of hepatitis B and C. These interferons bind to the IFN-α/β receptor (IFNAR) and are produced in response to viral infections, triggering a cascade of antiviral responses [23]. Type II interferon, represented by IFN-γ, is involved in immune regulation and is primarily produced by

T helper cells and natural killer cells. IFN-γ plays a key role in modulating immune responses and enhancing the activity of macrophages and other immune cells [24]. Type III interferons, including IFN-λ, are emerging as a promising alternative in antiviral therapy. IFN-λ targets liver-specific receptors, which may reduce systemic side effects compared to Type I IFNs, making it a potential candidate for treating viral hepatitis with improved tolerability [25]. Together, these interferons form a critical component of the body's defense mechanism against viral infections, with each type contributing uniquely to immune regulation and antiviral activity.

Interferon-based therapies cause a wide range of side effects that can significantly affect patients' quality of life and treatment adherence. Among the most common adverse effects are flu-like symptoms, including fever, myalgia, and arthralgia, which typically occur shortly after IFN injection and subside within weeks. These symptoms are often managed with paracetamol or NSAIDs, though caution is advised in patients with thrombocytopenia due to the risk of bleeding complications [26]. Gastrointestinal disorders, such as nausea, dry mouth, and weight loss, are also frequently reported, particularly in patients receiving ribavirin. Prokinetic agents like metoclopramide can help alleviate these symptoms, improving patient comfort during therapy [27]. Hematologic effects, including anemia, neutropenia, and thrombocytopenia, are common and may require interventions such as erythropoietin or granulocyte colony-stimulating factor (G-CSF) to manage these conditions. However, the impact of these interventions on treatment efficacy remains unclear [28].

Psychiatric adverse events are another significant concern, with depression, anxiety, and irritability occurring in 30-70% of patients. While severe depression and suicidal ideation are rare, they necessitate close monitoring and, in some cases, psychiatric intervention. Interestingly, pre-existing psychiatric conditions do not necessarily increase the risk of severe side effects, though they may complicate management [29]. Thyroid dysfunction is also prevalent, with hypothyroidism (3-10%) and hyperthyroidism (1-3%) being the most common manifestations. These conditions are typically managed with hormone replacement or β-blockers, respectively, and rarely require discontinuation of therapy [30]. Dermatologic effects, such as skin reactions, itching, and hair loss, are frequent but generally reversible. Severe reactions like lichen planus are rare but may require specialized dermatologic care [31].

Ophthalmologic complications, particularly ischemic retinopathy, are another potential side effect, though significant visual loss is uncommon. Regular ophthalmologic evaluations are recommended for patients on long-term interferon therapy to detect and manage these issues early [32]. Other effects, such as fatigue, cough, and dyspnea, are often linked to ribavirin-induced anemia and can significantly impact daily functioning. Weight loss, ranging from 6-10% over a 48-week treatment period, is also common but typically reversible after therapy cessation [33]. Collectively, these side effects highlight the need for careful patient monitoring and supportive care to optimize treatment outcomes and maintain patient adherence.

Efforts to reduce IFN-related side effects have led to the development of novel interferons like PEG-IFN lambda, which targets liver-specific receptors and shows promise in reducing systemic side effects [34]. However, the advent of DAAs has diminished the role of IFN in HCV treatment, though it remains relevant in resource-limited settings [35]. Ongoing research aims to optimize IFN-based therapies and explore their potential in combination with DAAs for improved patient outcomes.

Interferon-based therapies have played a crucial role in managing chronic hepatitis B and C. However, their use is limited by a high burden of side effects, including hematologic, psychiatric, and dermatologic complications. While novel interferons and DAAs offer improved tolerability and efficacy, understanding and managing IFN-related adverse effects remain essential for optimizing patient outcomes. This study aims to provide a comprehensive assessment of these side effects in patients with chronic liver disease.

Subjects and Methods

Study Design

This prospective observational study was conducted in the outpatient clinic of the gastrointestinal center at Merjan Teaching Hospital from January 2024 to January 2025. A total of 127 patients initially met the study criteria, but 7 patients declined participation, 5 were lost to follow-up, and 1 patient died during the study period. These individuals were excluded from the final analysis, resulting in a cohort of 114 patients. Of these, 53 were diagnosed with chronic hepatitis B (CHB), and 61 had chronic hepatitis C (CHC). All participants were followed up over a three-month period to assess the side effects of interferon therapy.

Inclusion and Exclusion Criteria

Patients were included in the study if they met specific criteria. For hepatitis B, inclusion required the presence of hepatitis B surface antigen (HBsAg) in serum for at least 12 months, evidence of active viral replication (positive HBV-DNA in serum), and an age above 18 years. Exclusion criteria were designed to minimize confounding factors and included evidence of decompensated liver disease (e.g., ascites, variceal hemorrhage, or hepatic encephalopathy), serious comorbid medical conditions (e.g., diabetes mellitus, chronic renal failure, or connective tissue disease), known thyroid dysfunction, polypharmacy (except for ribavirin in hepatitis C cases, which was retained for ethical reasons), a history of major psychiatric illness or substance abuse, and age below 18 years. These exclusions ensured that the observed side effects could be attributed primarily to interferon therapy rather than other underlying conditions.

Study Procedures

After obtaining verbal consent, baseline investigations were conducted, including laboratory tests such as complete blood count, liver function tests, kidney function tests, and thyroid profiles. Anemia was defined according to WHO criteria as hemoglobin levels <13 g/dL in males and <12 g/dL in females. Neutropenia, lymphopenia, and thrombocytopenia were defined as absolute neutrophil counts <1,500/µL, lymphocyte counts <800/µL, and platelet counts <150,000/µL, respectively. Neuropsychological assessments were performed using the Montgomery-Asberg Depression Rating Scale (MADRS) to monitor depressive symptoms and mood changes during interferon therapy. The MADRS evaluates symptoms such as mood, sadness, tension, sleep disturbances, appetite changes, energy levels, concentration, suicidal ideation, and restlessness. Scores

were categorized as mild (0–6), moderate (7–19), or severe (≥20), with a score above 33 indicating severe depressive syndrome.

Patients were administered the standard dose of PEGASYS® (peginterferon alfa-2a) at 180 µg (0.5 mL) subcutaneously once weekly. They were interviewed at the start of the study and at three-month intervals using a structured questionnaire designed to collect demographic data (e.g., name, age, residence) and information on treatment duration, diagnosis date, and systemic symptoms. Patients were encouraged to report any adverse effects, which were graded as mild (not requiring consultation or affecting quality of life), moderate (requiring consultation and symptomatic treatment), or severe (necessitating dose reduction or discontinuation of therapy).

Follow-Up and Data Collection

Participants were monitored every four weeks after enrollment for a median observation period of 7.0 months, with follow-up ranging from 3.0 to 12.0 months. Laboratory tests, including liver function tests, hematologic parameters, and virologic markers, were measured monthly. Five patients were lost to follow-up, and one died before the study concluded. The final follow-up date for this study was January 20, 2015.

Data Analysis

Data were analyzed using the SPSS statistical package (version 15). Clinical characteristics were compared using the student's t-test, and Pearson's moment-product correlation coefficients were calculated to evaluate relationships between variables. The chi-square (χ^2) test was employed for categorical data, with Fisher's exact test or the Mid-P exact test used when expected values were less than 5. Continuous variables were compared using the t-test. A 95% confidence interval was applied, and a p-value of <0.05 was considered statistically significant. This comprehensive approach ensured robust analysis of the data, enabling accurate assessment of interferon-related side effects in patients with chronic hepatitis B and C.

Results

Demographic and Clinical Characteristics

Among the 114 eligible patients receiving interferon (IFN) therapy, 66 (57.9%) were male, and 48 (42.1%) were female. Of these, 53 (46.4%) had chronic hepatitis B (CHB), while 61 (53.6%) had chronic hepatitis C (CHC). The age of participants ranged from 20 to 60 years, with a mean age of 39.6 years (Fig 1).

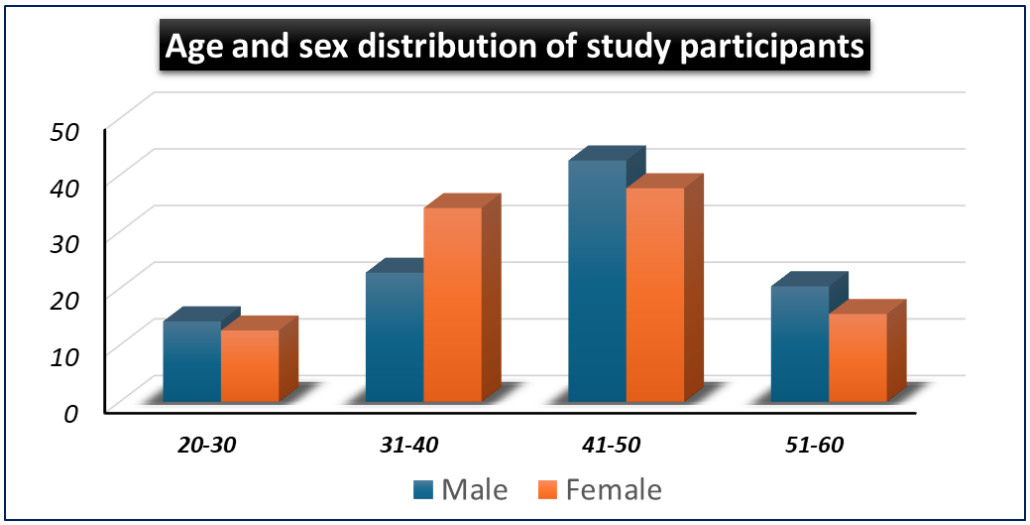

Fig 1: Age and sex distribution of study participants, N=114

Laboratory Profile

Table 1 presents the laboratory profile of the study participants at baseline and after 3–6 months of IFN therapy. Significant changes were observed in hemoglobin (Hb) levels, which decreased from 13.81 ± 1.28 g/dL to 12.02 ± 1.38 g/dL (p = 0.000), and liver enzymes, with alanine aminotransferase (ALT) increasing from 38.2 ± 7.61 U/L to 45.9 ± 23.71 U/L (p = 0.013) and aspartate aminotransferase (AST) rising from 31.2 ± 7.6 U/L to 42.87 ± 16.96 U/L (p = 0.011). No significant changes were noted in platelet counts, thyroid-stimulating hormone (TSH), or creatinine levels (p > 0.05).

Table 1: Laboratory profile of the studied group. N=114

Variable	1st check	After 3-6 months	T test	P value
Hb	13.81±1.28	12.02±1.38	4.168	0.000
Platelets Count	165.3±27	177.4±28.16	1.594	0.118
TSH	1.72±0.44	1.63±0.58	-3.327	0.138
ALT	38.2±7.61	45.9±23.71	2.653	0.013
AST	31.2±7.6	42.87±16.96	2.512	0.011
Creatinine	0.76±0.21	0.82±0.1678	3.042	0.101

Adverse Effects of Interferon Therapy

Approximately 95% of patients experienced at least one adverse event during IFN therapy, with most being mild to moderate in severity (Table 2). The duration of therapy ranged from 1 to 19 months, and adverse events persisted throughout the treatment period.

Table 2: side effects observed during Interferon treatment, N=114

Adverse Effects	Frequency	Percentage
Hematological side effects	93	81.5
Anemia	75	66
Leukopenia	62	54
Thrombocytopenia	68	60
Flu like symptoms	104	91.2
Fever	81	71
Fatigue	75	66
Headache	73	64
Myalgia	65	57
Arthralgia	36	32
Skin side effects	24	21.05
Photosensitivity	18	16
Alopecia	6	05
Itching	22	19
Rashes	21	18
Gastrointestinal side effects	60	88.5
Nausea	41	36
Anorexia	58	51
Dyspepsia	38	33
Constipation	7	06
Neuropsychiatric side effects	39	34.2
Insomnia	37	33
Irritability	25	22
Depression	22	19
Anxiety	34	30
Emotional instability	10	09
Tremor	12	10
Suicide ideas	0	00
Local reaction at the site of injection	17	15
Erythema at site of injection	17	15
Injection abscesses	3	03
Respiratory symptoms	16	14
Cough	13	11
Shortness of breath	10	09
Chest pain	5	04
Thyroid dysfunction	5	04
Hypertension	9	08
Palpitation	26	23
Dry mouth	15	13
Loss of libido	6	05
Dysuria	15	13
Weight loss	26	23
Menstrual disorder	10	09
Dizziness	45	40

1. Flu-like Symptoms

Flu-like symptoms topped the list, affecting 91.2% (n=104) of patients (Table 2). These included fever (71%), headache (64%), fatigue (66%), myalgia (57%), and arthralgia (32%).

2. Hematological Side Effects

Hematological abnormalities were observed in 81.5% (n = 93) of patients. Mild to moderate anemia (Hb > 8.5 g/dL) was reported in 66% (n = 75), leukopenia in 54% (n = 62), and asymptomatic thrombocytopenia (platelet count > 50,000/µL) in 60% (n = 68).

3. Neuropsychiatric Side Effects

Neuropsychiatric symptoms were noted in 34.2% (n = 39) of patients, including insomnia (33%), irritability (22%), anxiety (30%), emotional instability (9%), depression (19%), and tremor (10%). No cases of suicidal ideation were reported.

4. Gastrointestinal Side Effects

Gastrointestinal symptoms affected 88.5% (n = 101) of patients, with nausea (55%), anorexia (51%), dyspepsia (33%), and constipation (6%) being the most common.

5. Dermatological Side Effects

Dermatological reactions were reported in 21.05% (n = 24) of patients, including photosensitivity (16%), itching (19%), skin rashes (18%), and alopecia (5%). Local injection site reactions, such as erythema (15%) and abscesses (2.6%), were also observed.

6. Other Side Effects

Additional adverse effects included respiratory symptoms (14%), thyroid dysfunction (4%), hypertension (8%), palpitations (23%), dry mouth (13%), loss of libido (5%), dysuria (13%), weight loss (23%), menstrual disorders (9%), and dizziness (40%).

Severe Adverse Events

One patient died due to liver failure and sepsis during IFN therapy. Life-threatening side effects, such as severe bone marrow suppression (granulocytes < 500/mm³ or platelets < 25,000/mm³), were observed in six patients. These symptoms resolved completely after discontinuation of IFN therapy.

Relationship Between Adverse Effects and Treatment Duration

Four adverse effects showed a significant correlation with the duration of IFN therapy: arthralgia ($p = 0.007$), palpitations ($p = 0.035$), itching ($p = 0.035$), and rash ($p = 0.005$). Patients experiencing these symptoms had a longer mean duration of therapy compared to those without symptoms (Table 3).

Table 3: the statistical data of side effects with significant relation to duration of treatment according to current study.

	Positive cases		Negative cases		P value
	Mean of duration (months)	Standard deviation	Mean of duration (months)	Standard deviation	
Palpitation	7.08	5.482	5.61	4.474	0.035
Arthralgia	8.1	4.933	4.7	2.627	0.007
Itching	6.18	5.812	6.2	3.657	0.035
Rash	8.9	5.383	5.33	3.425	0.005

Gender-Related Adverse Effects

Two side effects were significantly associated with gender: dizziness and hypertension. Dizziness was more prevalent in males (76.7%) than females (24.3%) ($\chi^2 = 0.012$). Conversely, new-onset hypertension was more common in females (7 out of 9 cases) ($\chi^2 = 0.018$) (Fig 2).

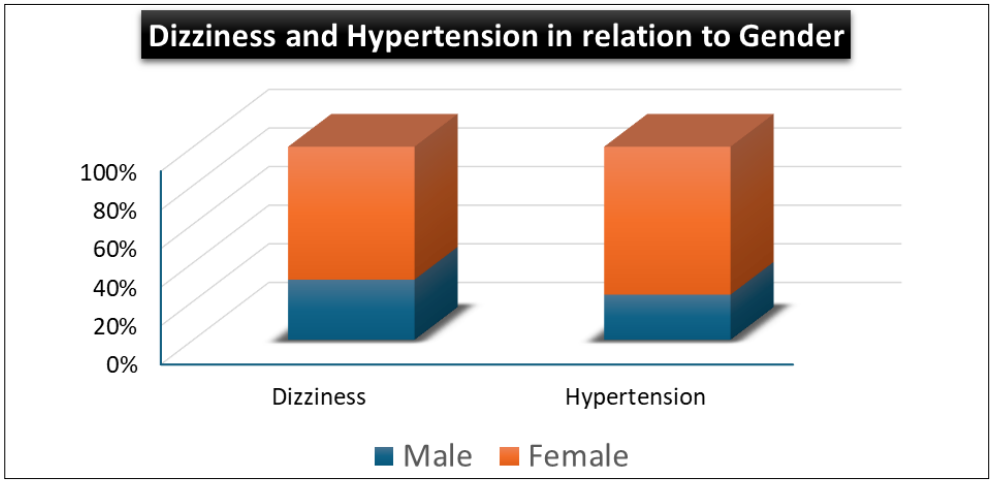

Fig 2: Dizziness and Hypertension in relation to Gender, N=114

Hepatitis Type-Related Adverse Effects

Tremor and anemia were significantly associated with the type of hepatitis. Tremor was more frequent in CHB patients (75% of cases, n = 9) compared to CHC patients (n = 3) ($\chi^2 = 0.042$). Conversely, anemia was more prevalent in CHC patients (93.3% of cases, n = 70) than in CHB patients (6.6%, n = 5) ($\chi^2 = 0.005$) (Fig 3).

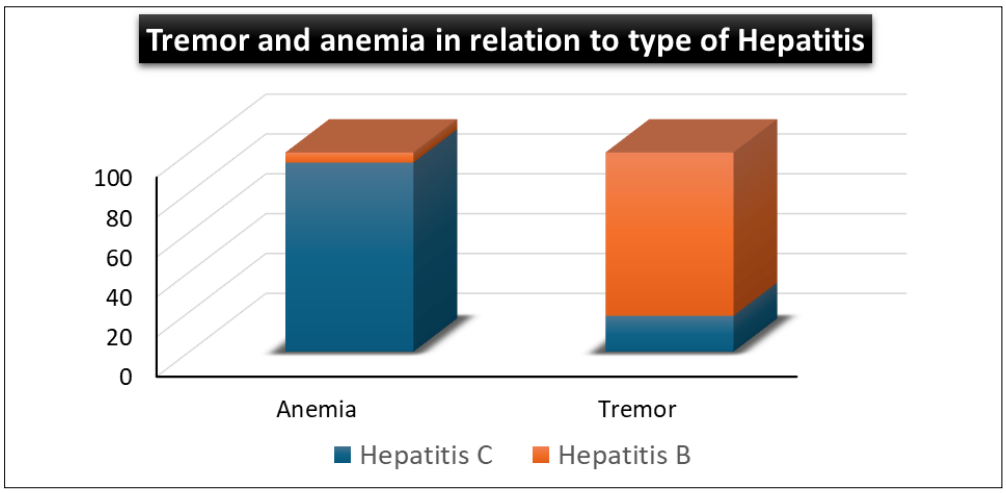

Fig 3: Tremor and Anemia in Relation to Hepatitis Type, N=114

Discussion

The findings of this study provide a comprehensive overview of the demographic, clinical, and laboratory characteristics of patients undergoing interferon (IFN) therapy for chronic hepatitis B (CHB) and chronic hepatitis C (CHC), as well as the associated adverse effects. The results highlight the high prevalence of side effects, their relationship with treatment duration, and variations based on gender and hepatitis type. These findings are consistent with previous studies and contribute to the growing body of evidence on the challenges of IFN therapy.

Demographic and Clinical Characteristics

The study population comprised 114 patients, with a slight male predominance (57.9%) and a mean age of 39.6 years. This demographic profile aligns with global trends, where chronic viral hepatitis disproportionately affects middle-aged individuals, often with a higher prevalence in males due to differences in exposure and healthcare-seeking behavior [36]. The distribution of CHB (46.4%) and CHC (53.6%) reflects the regional epidemiology of viral hepatitis, where both HBV and HCV remain significant public health concerns [37].

Laboratory Profile

Significant changes in laboratory parameters were observed during IFN therapy. Hemoglobin (Hb) levels decreased significantly ($p = 0.000$), consistent with the known myelosuppressive effects of IFN, particularly when combined with ribavirin in CHC patients [38]. The increase in ALT and AST levels ($p = 0.013$ and $p = 0.011$, respectively) may reflect immune-mediated liver inflammation, a common phenomenon during IFN therapy as the immune system targets infected hepatocytes [39]. The absence of significant changes in platelet counts, TSH, and creatinine levels suggests that these parameters are less affected by IFN therapy, although close monitoring remains essential.

Adverse Effects of Interferon Therapy

Approximately 95% of patients experienced at least one adverse event, underscoring the challenging tolerability profile of IFN therapy. The most common side effects were flu-like symptoms (91.2%), hematological abnormalities (81.5%), and gastrointestinal symptoms (88.5%). These findings are consistent with previous studies, which have reported similar rates of IFN-related adverse effects (40, 41).

1. Flu-like Symptoms

The high prevalence of flu-like symptoms, including fever (71%), headache (64%), and fatigue (66%), is well-documented in the literature. These symptoms are thought to result from the systemic immune activation induced by IFN, particularly the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [42].

2. Hematological Side Effects

Hematological abnormalities, including anemia (66%), leukopenia (54%), and thrombocytopenia (60%), are common due to IFN's myelosuppressive effects. Anemia was significantly more prevalent in CHC patients, likely due to the additional hemolytic effect of ribavirin [43]. Thrombocytopenia, though often asymptomatic, requires careful monitoring to prevent bleeding complications.

3. Neuropsychiatric Side Effects

Neuropsychiatric symptoms, such as insomnia (33%), depression (19%), and anxiety (30%), were reported in 34.2% of patients. These effects are attributed to IFN's impact on neurotransmitter systems, particularly serotonin and dopamine, which regulate mood and cognition [44]. The absence of suicidal ideation in this cohort is encouraging, though close psychiatric monitoring remains critical.

4. Gastrointestinal and Dermatological Side Effects

Gastrointestinal symptoms, including nausea (55%) and anorexia (51%), and dermatological reactions, such as itching (19%) and skin rashes (18%), were frequently reported. These side effects are consistent with previous studies and are often manageable with supportive care [45].

5. Other Side Effects

Less common but notable side effects included thyroid dysfunction (4%), hypertension (8%), and dizziness (40%). The gender-specific association of dizziness (more common in males) and hypertension (more common in females) warrants further investigation to understand the underlying mechanisms.

Severe Adverse Events

One patient died due to liver failure and sepsis, highlighting the potential for life-threatening complications during IFN therapy. Severe bone marrow suppression, observed in six patients, resolved after IFN discontinuation, emphasizing the importance of timely intervention in such cases [46].

Relationship Between Adverse Effects and Treatment Duration

The study identified a significant correlation between treatment duration and specific adverse effects, including arthralgia ($p = 0.007$), palpitations ($p = 0.035$), itching ($p = 0.035$), and rash ($p = 0.005$). These findings suggest that prolonged IFN therapy may exacerbate certain side effects, necessitating individualized treatment plans and close monitoring [47].

Gender and Hepatitis Type-Related Adverse Effects

Gender-specific differences were observed, with dizziness more prevalent in males and hypertension more common in females. These findings align with previous studies suggesting that hormonal and physiological differences may influence the manifestation of IFN-related side effects [48]. Additionally, tremor was more frequent in CHB patients, while anemia was more prevalent in CHC patients, likely due to the combined effects of IFN and ribavirin in CHC treatment [49].

Clinical Implications

The widespread adverse effects highlight the need for proactive management, including patient education, regular monitoring, and timely intervention. The use of growth factors (e.g., erythropoietin for anemia) and dose adjustments may help mitigate some side effects. Additionally, the development of novel therapies, such as direct-acting antivirals (DAAs) for HCV and newer immunomodulators for HBV, offers hope for reducing reliance on IFN-based regimens [50].

Limitations

This study has several limitations, including its single-center design and relatively small sample size. The observational nature of the study limits the ability to establish causal relationships. Future multicenter studies with larger cohorts are needed to validate these findings and explore the underlying mechanisms of IFN-related adverse effects.

Conclusion

This study highlights the significant burden of adverse effects associated with IFN therapy in patients with chronic hepatitis B and C. The findings emphasize the importance of individualized treatment plans, close monitoring, and supportive care to improve patient outcomes. As newer therapies become available, the role of IFN may diminish, but understanding its side effects remains critical for optimizing the management of chronic viral hepatitis.

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