Risk of infections during interferon-based treatment in patients with chronic HCV infection and advanced hepatic fibrosis

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jgh.12929

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Tables and figures: 5 tables and 3 figures (including 1 supplementary table and 1 supplementary figure)

Word count abstract: 254 words

Word count manuscript: 3983 words

List of abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; DAAs, direct-acting antivirals; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; OR, odds-ratio; PegIFN, pegylated interferon; RBV, ribavirin; SVR, sustained virological response

Author contributions

Study coordination and design, data collection, data analysis, writing of manuscript, approval of final version: RM, AJM

Study coordination and design, data collection, critical review of the manuscript, approval of final version: BJV, RJK

Data collection, critical review of the manuscript, approval of the final version: JJF, HW, J-FD, FL, MPM, SZ, HLAJ

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RM, AJM, BEH, RJK and BJV had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Financial support

The study was not sponsored by third parties in the sense of industrial partners. The study was funded by the Foundation for Liver and Gastrointestinal Research in Rotterdam. This foundation was established in 1985 as an institution without purpose of financial gain and has the mission to stimulate scientific research in the field of diseases of the liver and the gastrointestinal tract. A major part of its activities are undertaken at the Erasmus MC in Rotterdam, the Netherlands.

Disclosures

Drs. Maan received financial compensation for consultancy activities from AbbVie. Drs van der Meer received financial compensation for lecture activities for MSD and Gilead. Dr. Feld received financial compensation for consultancy, and development of educational presentation activities from AbbVie, BMS, Merck, Gilead and Janssen and his institution received grants from Abbvie, Boehringer-Ingelheim, Gilead and Santaris. , and. Dr Wedemeyer received financial compensation for consultancy and/ or lecture activities from Roche, MSD, Abbott, Novartis,

Bristol Myers Squibb, and Gilead, and his institution received grants from Roche, Merck Sharpe & Dohme, Abbott, Novartis, Bristol Myers Squibb, and Gilead. Dr Manns received financial compensation for consultancy and/ or lecture activities from Roche, Bristol Myers Squibb, Gilead, Boehringer Ingelheim, Novartis, Merck, Janssen, and GlaxoSmithKline, and research grants from Roche, Gilead, Novartis, Boehringer Ingelheim, Bristol Myers Squibb, Merck, and Janssen. Dr Zeuzem received financial compensation for consultancy and/ or lecture activities from Abbott, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Gilead, Merck, Novartis, Roche, Santaris, Janssen, and Vertex. Dr Janssen received financial compensation for consultancy activities and/ or payment for lectures from Roche, Merck, Abbott, Santaris, Anadys, Medtronic, Tibotec, Bristol Myers Squibb, and Gilead, and his institution received grants from Roche, Merck, Abbott, Santaris, Anadys, Medtronic, and Tibotec. Dr. de Knegt reported that his institution received financial compensation for consultancy activities and/ or lecture activities from Merck, Janssen, Roche, Gilead, and Medtronic, and research grants from Merck and Roche. Dr Veldt received financial compensation for a board membership at GlaxoSmithKline and Janssen Therapeutics.

ABSTRACT

Background & Aims. Pegylated interferon-based treatment is still the backbone of current hepatitis C therapy and is associated with bone marrow suppression and an increased risk of infections. The aim of this retrospective cohort study was to assess the risk of infections during interferon-based treatment among patients with chronic HCV infection and advanced hepatic fibrosis and its relation to treatment-induced neutropenia.

Methods. This cohort study included all consecutive patients with chronic HCV infection and biopsy-proven bridging fibrosis or cirrhosis (Ishak 4-6) who started treatment between 1990 and 2003 in five large hepatology units in Europe and Canada. Neutrophil counts between 500/µL-749/µL and below 500/µL were considered as moderate and severe neutropenia, respectively.

Results. This study included 723 interferon-based treatments, administered to 490 patients. In total, 113 infections were reported during 88 (12%) treatments, of which 24 (21%) were considered severe. Only one patient was found to have moderate neutropenia and three patients were found to have severe neutropenia at the visit before the infection. Three hundred and twelve (99.7%) visits with moderate neutropenia and 44 (93.6%) visits with severe neutropenia were not followed by an infection. Multivariable analysis showed that cirrhosis (OR 2.85, 95%CI 1.38-5.90, p=0.005) and severe neutropenia at the previous visit (OR 5.42, 95%CI 1.34-22.0, p=0.018) were associated with the occurrence of infection, while moderate neutropenia was not. Among a subgroup of patients treated with PegIFN, severe neutropenia was not significantly associated (OR 1.63, 95%CI 0.19-14.2, p=0.660).

Conclusions. In this large cohort of patients with bridging fibrosis and cirrhosis, infections during interferon-based therapy were generally mild. Severe interferon-induced neutropenia rarely occurred, but was associated with on-treatment infection. Moderate neutropenia was not associated with infection, suggesting that current dose reduction guidelines might be too strict.

Keywords: Chronic hepatitis C; Antiviral treatment; Cirrhosis; Neutropenia; Infections; Side effects

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of cirrhosis, hepatocellular carcinoma (HCC) and end-stage liver disease (1). It has been estimated that by 2030, 45% of the US patients chronically infected with HCV will have cirrhosis (2). Today, antiviral treatment efficacy among patients with cirrhosis is unsatisfactory (3-5). Although it is expected that even in this difficult-to-treat subgroup of patients the sustained virological response (SVR) rates will improve substantially by using interferon-free regimes (6-8), pegylated interferon (PegIFN) and ribavirin (RBV) are still the backbone of antiviral therapy in most countries. In fact, due to the high costs of the new direct-acting antivirals (DAAs), PegIFN and RBV might remain the primary treatment option for many patients with chronic HCV infection around the globe. Treatment with PegIFN is, however, associated with major side-effects, of which bone marrow suppression and subsequent neutropenia is one of the most frequently reported. Out of concern for infections, product labels and guidelines currently advise physicians to reduce the dose of PegIFN when neutrophil counts drop below 750/µL and to stop PegIFN when neutrophil counts drop below 500/µL (9, 10). This is largely based on prior experiences in oncology, where patients receiving chemotherapy showed an increased risk of infection when neutrophil counts dropped below 500/µL, with the greatest risk below 100/µL (11). While patients undergoing interferon-based therapy are indeed more susceptible to bacterial and fungal infections, prior studies did not find these to be related to the treatment-induced neutropenia (12-15). Especially because interferon dose adjustments compromise antiviral treatment efficacy for patients with chronic HCV infection, it was suggested that the current guidelines regarding dose reductions might be too strict (16, 17). However, whereas patients with cirrhosis are considered to be immunocompromised and thus at the highest risk of infections, data regarding the relation between neutropenia and infections during interferon-based antiviral therapy within this population are scarce.

PATIENTS AND METHODS

Patients. The current study is based on all patients included in our previously described international, multicenter cohort (18). This cohort included all consecutive patients from 5 large hepatology units in Europe and Canada, who had chronic HCV infection and started an interferon-based treatment between 1990 and 2003. They all had histological proof of bridging fibrosis (Ishak fibrosis score 4) or cirrhosis (Ishak fibrosis score 5 or 6) (19). Patients co-infected with the human immunodeficiency virus or the hepatitis B virus were excluded, as well as patients with a history of decompensated liver disease. For the current study all consecutive treatment courses with available on-treatment data, including assessment of infection and laboratory results, were included.

All charts were re-reviewed by a single investigator (RM) in order to collect detailed baseline and on-treatment data. Data were obtained on patient characteristics (age, gender, body mass index [BMI]), severity of liver disease (Ishak fibrosis score), presence of diabetes mellitus (DM), severe alcohol use and antiviral treatment (type of medication, treatment period, previous and current virological response). Furthermore, laboratory data (neutrophil count, platelet count, hemogblobin, albumin, bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT] and glucose) and virology data (HCV genotype, HCV RNA and anti-hepatitis B core antigen) were collected. The period within six months before treatment was considered as baseline. During antiviral treatment, all (Peg-)interferon and/or RBV dose reductions or treatment cessations were collected as well as all infectious episodes and all other adverse events.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol was reviewed and approved by the ethics committee in the center of the primary investigators, which was the Erasmus Medical Center in Rotterdam, the Netherlands. Ethical approval in the participating centers was obtained according to the local regulations.

Outcome measures. The primary outcome measure was the occurrence of infections during antiviral therapy or within two weeks after treatment cessation. Secondary outcome measures were on-treatment neutropenia and the severity of infections.

Neutrophil counts from 500/µL to 749/µL were defined as moderate neutropenia, since interferon dose reductions are advised at these levels. Neutrophil counts below 500/µL were considered as severe neutropenia. Diabetes mellitus at baseline was defined by an elevated fasting glucose (>6.1 mmol/L), a positive glucose tolerance test or if patients were using anti-diabetic medication.

Infections were considered as all the episodes of clinically suspected infection according to the treating physician, when antibiotic therapy was prescribed or when there was evidence of an infection (radiology, positive culture). Severe infections were defined as infections resulting in death, hospital admission or treatment discontinuation. All other infections were defined as mild.

Statistical analyses. Continuous variables were summarised as median (interquartile range [IQR]) and categorical variables as frequencies (percentages). Comparisons between groups were performed using X^2 test for categorical variables or the Mann-Whitney U test for continuous variables.

The dynamics of neutrophil counts during treatment for different groups were studied with a repeated measurement model. A restricted cubic spline was fitted per group and to take into account multiple measurements per patient during treatment a model with random intercept and slope was applied.

Logistic regression was used to assess which baseline factors were associated with the occurrence of infections during antiviral therapy. Age, sex, cirrhosis, DM and variables with a p-value of ≤ 0.2 in univariable analyses were included in multivariable analyses. Adjusting for multiple measurements within a patient, the association between on-treatment neutrophil counts

and succeeding infectious events was assessed. By using a backward stepwise method we selected the variables significantly associated with infections and included these in the final model. Akaike's Information Criteria were used to select the best model. A sensitivity analysis was performed among only those patients treated with PegIFN-based regimens, since standard interferon is not used nowadays. Another sensitivity analysis was performed among only those patients with cirrhosis, since these patients are at the highest risk of infection.

The cumulative incidence of infections was assessed using the Kaplan-Meier method. The log-rank test was applied to compare patients with bridging fibrosis and cirrhosis.

A p-value <0.05 was considered statistically significant and all statistical tests were two-tailed. The significance level of interactions was set at 0.01 in order to correct for multiple testing (18). PASW statistics 21.0 for Windows (SPSS, IBM, Armonk, New York, USA) and SAS 9.3 were used.

RESULTS

Patients. Overall, 546 patients with chronic HCV infection and bridging fibrosis or cirrhosis started interferon-based antiviral therapy between 1990 and 2003. In 490 (90%) patients detailed on-treatment data were available to assess the occurrence of infections during at least one interferon-based regimen. Of the 361 (74%) patients without SVR, 174 received at least one subsequent antiviral treatment regimen. Overall, 723 treatment courses could be included in the analyses. Table 1 summarizes the baseline characteristics of the patients at their first included treatment. Median age was 49 years (IQR 43–56), 336 (69%) patients were male and 372 (76%) presented with cirrhosis.

Neutropenia and dose of interferon. The median neutrophil count prior to the start of all treatment courses was 3000/µL (IQR 2400–3900). Median time between visits was 2 weeks (IQR 1–4 weeks). During therapy the median neutrophil count decreased to a nadir of 1200/µL (IQR 800–1700) in a median time of 11 weeks (IQR 4–22). Patients receiving PegIFN had a lower median nadir neutrophil count as compared to patients receiving standard interferon (1000/µL [IQR 700–1400] versus 1400/µL [IQR 1000–2000], p<0.001), whereas baseline neutrophil counts did not differ between these groups (p=0.729). Figure 1 shows the course of neutrophil counts during treatment. During 88 (12%) treatment courses moderate neutropenia occurred at least once, and during 23 (3%) treatment courses severe neutropenia occurred at least once. Because of neutropenia, the (Peg-)interferon dose was reduced during 58 (8%) treatment courses and 3 (<1%) treatments were discontinued.

Infections. In total, 113 infections were reported during 88 (12%) treatments among 81 (17%) patients. Table 2 summarises the type of infections. Dermatological infections were most common (24%), followed by upper respiratory tract infections (20%) and urinary tract infections (18%). None of the patients were diagnosed with spontaneous bacterial peritonitis during

treatment. Median time until the first infection was 12 weeks (IQR 6–24). Time until infection was not significantly different for mild or severe infections (p=0.648). Twenty-four infections among 23 (3.2%) patients were defined as severe. Treatment was discontinued due to infection in 7 patients and 23 hospital admissions due to an infection were reported. The median duration of admission was 9 days (IQR 3–12). None of the patients died as a result of an on-treatment infection. During 92 (81%) of the infections, antibiotic therapy was prescribed.

Neutropenia and infections. Eleven patients (1.5%) had a baseline neutrophil count below 1500/µL, of which ten patients had a grade 2 neutropenia (i.e. neutrophil count <1500 /µL) and only one patients had a grade 3 neutropenia (i.e. neutrophil count <1000/µL). Three of these patients needed a dose reduction due to neutropenia, of which one patient discontinued due to side effects, and one of these patients needed dose reductions due to thrombocytopenia. In only one patient an infection was reported, which was severe. This patient required hospital admission for 23 days due to a *Staphylococcus aureus* bacteremia following cellulitis. The infection resolved with intravenous antibiotics, while interferon and RBV were continued.
For 81 infections (72%) the neutrophil count at the visit prior to the infection was available. Median neutrophil count at the visit prior to an infection was 1740/µL (IQR 1300–2650). The median neutrophil count at the previous visit was not different for mild and severe infections (p=0.399). Only one patient was found to have moderate neutropenia (neutrophil count of 690/µL) and three patients were found to have severe neutropenia (neutrophil counts of 300/µL, 330/µL and 390/µL) at the visit before the infection. Three hundred and twelve (99.7%) visits with moderate neutropenia and 44 (93.6%) visits with severe neutropenia were not followed by an infection. Patients who underwent a dose reduction of (Peg-)interferon did not experience less infections, compared to patients who did not undergo a dose reduction (10.8% vs 10.6%, p=1.00). During nine treatment courses, dose reductions were performed after an infection was reported.

Table 3 summarizes the results of univariable logistic analysis, which showed that female gender (OR 1.58, 95%CI 1.01–2.47, p=0.044), the presence of cirrhosis (OR 2.14, 95%CI 1.19–3.85, p=0.011) and number of weeks on treatment (OR 1.01, 95%CI 1.00–1.02, p=0.032) were significantly associated with infection. While moderate neutropenia at the visit prior to infection was not significantly associated (OR 0.19, 95%CI 0.03–1.40, p=0.103) with infection, severe neutropenia at the previous visit was (OR 4.25, 95%CI 1.21–14.9, p=0.024).

Multivariable logistic analyses, adjusted for age, gender, DM, number of weeks on treatment and type of interferon, showed that cirrhosis (OR 2.85, 95%CI 1.38-5.90, p=0.005) and severe neutropenia at the visit prior to the infection (OR 5.42, 95%CI 1.34-22.0, p=0.018) were independently associated with infections. The interaction terms between the variables in the final model were not statistically significant.

In a sensitivity analysis including only the 356 (49%) PegIFN-based treatment courses among 292 patients, during which 71 infections were reported, severe neutropenia at the visit prior to infection was not significantly associated (OR 1.63, 95%CI 0.19-14.2, p=0.660). In this analysis cirrhosis (OR 3.22, 95%CI 1.16-8.95, p=0.025) was the only factor associated with infection.

Table 4 shows the variables associated with severe infection during antiviral treatment. After adjustment for age and cirrhosis, female gender (OR 3.94, 95%CI 1.54-10.1, p=0.004) and DM (OR 3.84, 95%CI 1.52-9.70, p=0.004) were associated with the occurrence of severe infections.

Figure 2 illustrated the infection rates according to the presence of cirrhosis or DM.

DISCUSSION

In this large cohort study, infections which occurred during interferon-based antiviral therapy were generally mild. The percentage of 12% of treatment courses complicated by infections is in line with previous studies reporting an infection rate of 4-23% (12, 14, 20, 21). Moderate (Peg-)interferon-induced neutropenia was not associated with infection, whereas severe neutropenia was. However, a sensitivity analysis among patients treated with PegIFN could not confirm this. Furthermore, approximately 94% of the visits of patients with severe neutropenia were not followed by an infection. Cirrhosis and diabetes were important risk factors for the occurrence and severity of infection.

This real-life study was not limited by strict interferon dose modification rules which are used in clinical trials and thereby allows for assessment of lower neutrophil counts in relation to infections. Severe neutropenia occurred during only 3% of antiviral treatment regimens and only four (17%) of these treatment courses with severe neutropenia were complicated by an infection. When only PegIFN-based regimens were considered, the association between severe neutropenia and occurrence of infections was not statistically significant. This is in line with the findings of Antonini et al. (21) who showed that neither the presence nor duration of neutropenia was associated with the occurrence of infections among 319 chronic HCV-infected patients treated with PegIFN and RBV. This was confirmed by another retrospective study among 321 PegIFN and RBV treated patients, as also in this study on-treatment neutropenia and its duration were not associated with infectious episodes (12). The IDEAL study is the largest clinical study to date, which prospectively assessed the role of PegIFN-induced cytopenias on the occurrence of infections (20). Again, no association between nadir neutrophil count and occurrence of infection was found. The authors did report, however, that the nadir lymphocyte count was associated with infectious episodes. Because the nadir lymphocyte count was analysed rather than the lymphocyte count at the most recent visit prior to infection, it remains

difficult to determine causality and to translate this finding into clinical recommendations with respect to the dose of PegIFN. In our cohort, lymphocyte counts were not available as these are not collected during antiviral therapy in daily practice.

In contrast to our cohort, the above described studies included a relatively low number of patients with advanced fibrosis (11-30%) and did not show results for this subgroup specifically. We found that patients with cirrhosis more frequently experienced infections during interferon-based therapy as compared to those with bridging fibrosis. Roomer et al. (12) also described a higher rate of infectious episodes among the 68 (21%) patients with cirrhosis included in their study, and from other cohorts, similar results were obtained with odds ratios ranging from 2.7-4.9 (12-15). Triple therapy regimens with DAAs were not included in our study and often reduce treatment duration to 12 or 24 weeks (22-24). Shortened PegIFN therapy could prevent infections, as we found a linear infection rate during treatment with a median of 12 weeks from initiation of therapy to the occurrence of an infection (Supplementary figure 1). However, first real-world data regarding the addition of telaprevir or boceprevir to PegIFN and RBV therapy indicate a substantially elevated risk of severe infections among patients with cirrhosis, likely because patients with advanced cirrhosis who would have met stopping rules with PegIFN and ribavirin alone, were able to achieve viral suppression and stay on therapy longer, thus increasing their risk of infection (25). Cirrhosis is considered an immunocompromised state which may lead to a variety of infections, also outside of the scope of interferon-based therapy (26). Translational studies have suggested that patients with cirrhosis have impaired neutrophil function, limiting the first immunological defence against bacterial pathogens (27, 28).

As this cohort study included solely patients treated with an interferon-based regimen, it lacks a control group of untreated cirrhotic patients. However, a previous study among cirrhotic patients awaiting liver transplantation, found that there was a higher incidence of infections in the group that was treated with PegIFN and RBV compared to the matched control group that did not receive treatment, respectively 13 events and 2 events (p=0.012) (29). This study

indicated that PegIFN-based antiviral treatment increases the risk of bacterial infections in a cirrhotic population. Although apparently not through a reduction in neutrophil counts, infectious episodes are more frequently encountered during the use of interferon-based therapy. The mechanisms for this association are, however, not well understood. It has been hypothesized that PegIFN alters neutrophil function, but limited data are available (30). Others have suggested that PegIFN boosts other factors among cirrhotic patients which facilitate infections, such as bacterial translocation, dysfunction of the reticuloendothelial system and reduction of serum and ascitic fluid complement levels (31). Thus, an impaired function of the immune system might be responsible for the increased infection rate during interferon based therapy.

Current recommendations regarding PegIFN dose reductions are based on experience among cancer patients receiving chemotherapy (11). In this situation, however, other mechanisms such as mucosal damage and hampered organ function caused by the underlying disease play important roles in the susceptibility for infections as well. Dose reductions due to neutropenia may need to be carefully considered as long as the neutrophil counts remain stable between 500 and 750µ/L. Dose reductions reduce the chance to attain SVR, which is likely to affect clinical outcome (16, 17, 32). A study among African American and Caucasian American patients, in whom dose reductions were not undertaken until the neutrophil count dropped below 500/µL, did not report a higher rate of infections than expected (33). Our study further suggests that dose reductions could not prevent infectious episodes during antiviral therapy as the number of patients who underwent a dose reduction of (Peg-)IFN did not experience less infections (10.8% vs 10.6%). This should be interpreted with caution as dose reductions were at the discretion of the treating physicians and the number of infections could be higher if these dose reductions were not applied. The treating physicians could have applied dose reductions only to those patients that had a higher initial risk for infectious events. Due to its retrospective character, one could not really conclude that reductions of IFN could not affect the occurrence of infections. Ideally, one would design a randomized controlled trial with one group of patients

undergoing dose reductions and the other group continuing the dose despite low neutrophil counts (or other haematological adverse events). Such studies are however hardly feasible. One could also debate whether dose reductions were performed too late. Unfortunately we were unable to assess this issue. Dose reductions were not performed according to the guidelines, making it impossible to conclude on timing of dose reductions. Furthermore, dose reductions were also performed for other reasons than neutropenia.

Our finding of an association between DM and more severe infection was not unexpected. Higher infection rates among diabetic patients could be explained by vascular insufficiency, depressed leucocyte and natural killer cell function, as well as impaired antioxidant systems involved in antibacterial activity (34, 35). Others have previously shown that the risk of infections during PegIFN-based therapy was around two to three fold higher among patients with chronic HCV infection and DM (12, 15).

The association of female gender and the occurrence of severe infection was also seen in the largest prospective study that assessed the risk for infections during antiviral treatment (20). In this study, they found an increased incidence of urinary tract infections and Candida infections, partly explaining the finding. Furthermore, they also found an increased incidence of respiratory tract infections among women. This was also the case in our study, where more women required hospital admission due to respiratory tract infections. There was no higher incidence of infections of the urinary tract. Although the underlying mechanism of our findings is not clear, clinicians should be aware of a possible increased risk for severe infection among women treated with PegIFN and RBV.

A limitation of our study is that, due to its retrospective character, not all infections may have been reported. However, it is unlikely that severe infections, which are clinically most relevant, were missed. Also, there was heterogeneity in the treatment regimens administered, varying from interferon monotherapy to combination therapy with PegIFN and RBV. Because

neutrophil counts showed deeper declines with PegIFN, a sensitivity analysis was performed including only PegIFN-containing regimens.

In conclusion, patients with chronic HCV infection and bridging fibrosis and cirrhosis undergoing interferon-based therapy experience generally mild infections. Patients with cirrhosis are at elevated risk of interferon-associated infections and among patients with DM the course of infection seems to be more severe, indicating these groups should be carefully monitored. Although on-treatment severe neutropenia (<500/µL) might be associated with an elevated risk of infection, such deep declines in neutrophils do not frequently occur during PegIFN-based therapy. Furthermore this finding could not be confirmed among a subgroup of patients treated with PegIFN, which is used in current daily practice. Moderate neutropenia was not associated with an increased infection rate, suggesting that dose reductions due to neutropenia may need to be carefully considered as long as the neutrophil counts remain stable between 500 and 750µ/L. Current guidelines regarding PegIFN dose reductions might be too strict and may unnecessarily compromise the virological efficacy of interferon-based therapy.

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Legends to the figures

Figure 1.

Dynamics of the neutrophil counts during treatment. Panel A shows the dynamics of neutrophil counts among all patients. Panel B shows the dynamics of neutrophil counts among patients with bridging fibrosis and cirrhosis. Panel C shows the dynamics of neutrophil counts among patients treated with standard interferon and pegylated interferon ($p<.001$).

Figure 2.

The bars represent the percentage of treatments with at least one mild or severe infection among specific subgroups of patients based on the presence of cirrhosis and diabetes mellitus. Fifteen infections were reported among patients that had both cirrhosis and diabetes mellitus, of which 10 were mild infections and 5 were severe infections.

Supplementary figure 1.

Kaplan-Meier curve showing the occurrence of infection within the first 30 weeks of treatment within two groups based on the presence of cirrhosis.

Table 1. Baseline characteristics at first registered treatment

Variable (missing cases [%])	Patients (n=490)
Male	336 (69%)
Age, in years	49 (43–56)
BMI, in kg/m^2 *	26.5 (23.7–29.4)
HCV genotype	
1	316 (65%)
2	46 (9%)
3	79 (16%)
4	23 (5%)
Other/ unknown	26 (5%)
Treatment naïve	397 (81%)
Cirrhosis	372 (76%)
Fibrosis score	
Ishak 4	118 (24%)
Ishak 5	98 (20%)
Ishak 6	274 (56%)
Neutrophil count per µL *	3040 (2500–3900)
Platelet count, in 10^9/L	146 (108–197)
Albumin, in g/L *	42 (39–44)
Bilirubin, in µmol/L *	13 (10–19)
Treatment with PegIFN	201 (41%)
Treatment duration, in weeks	26 (21–48)
Diabetes mellitus	64 (13%)
Alcohol abuse ever *	109 (22%)

a. Abbreviations: PegIFN ; pegylated interferon

b. Medians are presented as number, (IQR, interquartile range). Numbers are presented as n, (percentage of the whole group)

c. Variables with an asterisk (*) had ≥10% missing values

Table 2. Type of infections

Type of infection	n (%)	Severe infection (%)[c]
Urinary tract	20 (18%)	3 (3%)
Upper respiratory tract	22 (20%)	2 (2%)
Pulmonary	15 (13%)	6 (5%)
Dermatological	27 (24%)	8 (7%)
Gastrointestinal	3 (3%)	2 (2%)
Oral	12 (11%)	1 (1%)
Other[b]	14 (12%)	2 (2%)
Total	113 (100%)	24 (21%)

a. Data presented as number, (percentage of the total number of infections)

b. Other infections included a case of endocarditis (severe), dental and eye infections

c. Severe infection was defined as infection requiring hospital admission or treatment discontinuation

Table 3. Logistic regression analysis for infection

Variable	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value	Multivariable (PegIFN only*) OR (95% CI)	p-value
Age	1.02 (1.00-1.04)	0.075	1.02 (0.99-1.05)	0.296	1.02 (0.99-1.06)	0.218
Female gender	1.58 (1.01-2.47)	0.044	1.67 (0.95-2.94)	0.077	1.03 (0.52-2.10)	0.913
BMI	1.03 (0.98-1.07)	0.263				
Cirrhosis at baseline	2.14 (1.19-3.85)	0.011	2.85 (1.38-5.90)	0.005	3.22 (1.16-8.95)	0.025
DM at baseline	1.58 (0.96-2.59)	0.073	1.48 (0.78-2.81)	0.224	1.17 (0.53-2.56)	0.694
Weeks on treatment	1.01 (1.00-1.02)	0.032	1.01 (0.99-1.02)	0.322		
Type of interferon (PegIFN vs standard interferon)	1.38 (0.88-2.16)	0.155	0.80 (0.45-1.41)	0.435		
Moderate neutropenia at previous visit (500-749/µL)	0.19 (0.03-1.40)	0.103				
Severe neutropenia at previous visit (<500/µL)	4.25 (1.21-14.9)	0.024	5.42 (1.34-22.0)	0.018	1.63 (0.19-14.2)	0.660
Absolute drop in neutrophil count, per 1/µL	0.98 (0.70-1.38)	0.924				
Relative drop in neutrophil count, per 1/µL[d]	1.01 (0.98-1.03)	0.620				
Platelet count ≤ 100 * 10^9/L	0.86 (0.49-1.50)	0.589				
Albumin < 35 g/L	1.36 (0.59-3.15)	0.471				

a. Abbreviations: BMI, body mass index; DM, Diabetes mellitus; PegIFN, pegylated interferon

b. All analyses were corrected for multiple measurements within a patient

c. * PegIFN based therapy, including 25 treatments with PegIFN monotherapy

d. Relative neutrophil drop is defined as the absolute drop in neutrophil count / baseline neutrophil count

Table 4. Logistic regression analysis for severe infection*

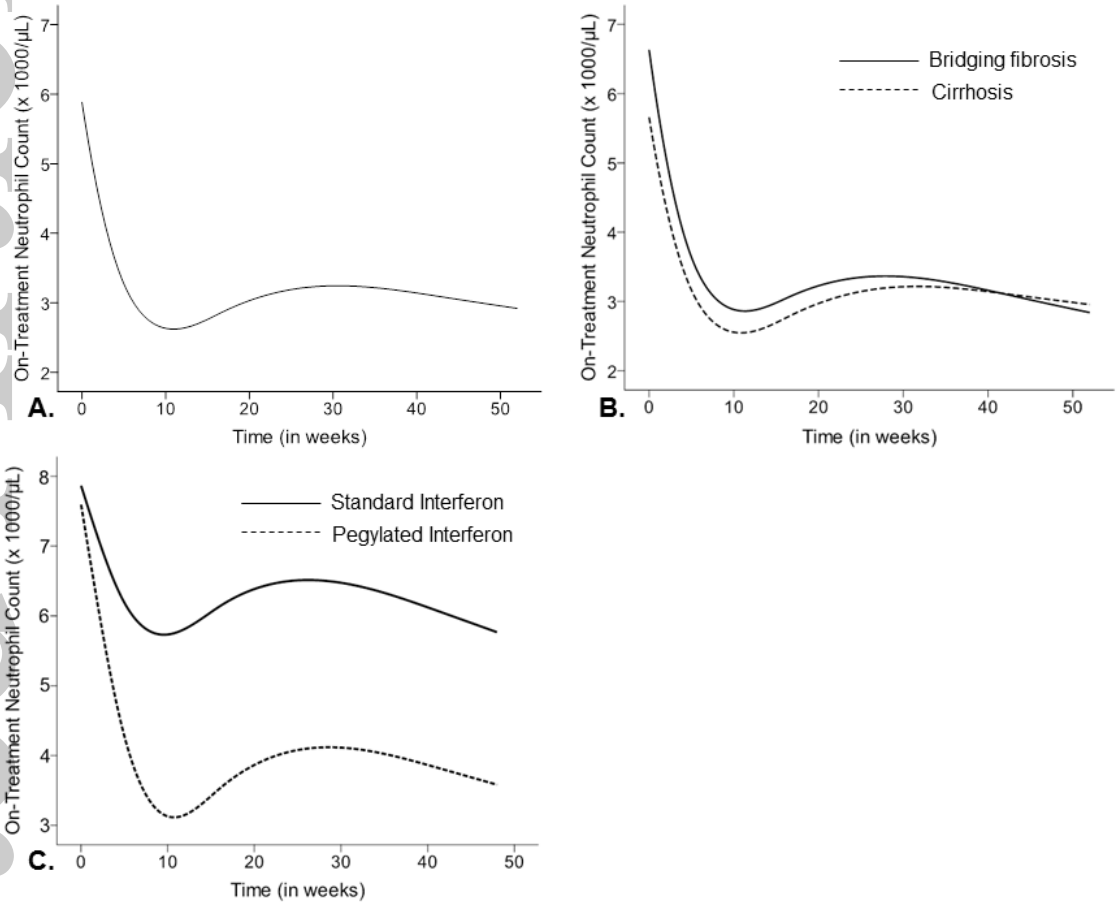
Variable#	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Age	1.01 (0.97-1.06)	0.572	1.00 (0.95-1.05)	0.942
Female gender	3.63 (1.41-9.34)	0.008	3.94 (1.54-10.1)	0.004
BMI	0.98 (0.87-1.11)	0.759		
Cirrhosis at baseline	1.47 (0.50-4.36)	0.484	1.23 (0.40-3.77)	0.721
DM at baseline	3.04 (1.29-7.20)	0.011	3.84 (1.52-9.70)	0.004
Weeks on treatment	0.89 (0.72-1.10)	0.280		
Type of interferon (PegIFN vs standard interferon)	0.80 (0.34-1.87)	0.600		
Baseline neutropenia	1.02 (0.76-1.36)	0.920		
Platelet count ≤ 100 * 10^9/L	1.52 (0.58-4.00)	0.396		
Albumin < 35 g/L	2.45 (0.69-8.65)	0.164		

a. Abbreviations: BMI, body mass index; DM, Diabetes mellitus; PegIFN, pegylated interferon

b. All analyses were corrected for multiple measurements within a patient

c. * Severe infections were defined as infections were treatment was discontinued or when admission was needed

d. # There were too few cases with moderate (n=1) or severe (n=1) neutropenia and severe infection to include these variables in the analysis.



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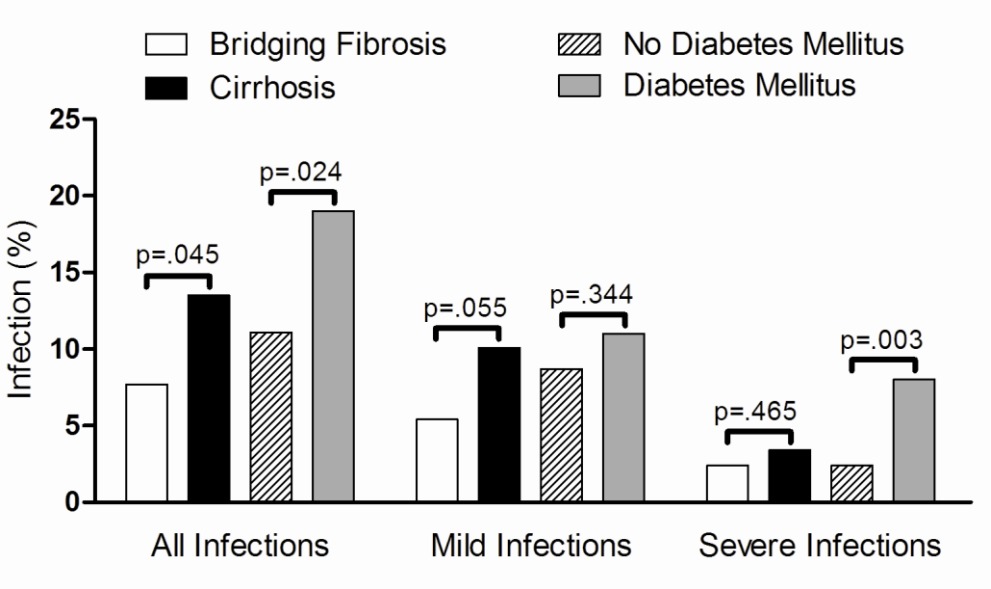

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