Hepatitis C treatment at three Norwegian hospitals 2000–2011

BACKGROUND In the period 2000–2011, chronic hepatitis C virus infection (HCV infection) was primarily treated with a combination of pegylated interferon and ribavirin. New antiviral drugs, which are effective but very expensive, are in the process of replacing this regimen. We have investigated the results pegylated interferon and ribavirin have yielded in ordinary clinical practice and examined the part this treatment may play in the near future.

MATERIAL AND METHOD We included in this retrospective study HCV-RNA-positive, treatment-naive patients at Stavanger University Hospital, Akershus University Hospital and Østfold Hospital who received at least one dose of pegylated interferon in combination with ribavirin in the period 2000–2011. The primary endpoint was sustained virologic response (SVR). Predictors for SVR were identified by means of logistic regression analysis.

RESULTS Of 588 included patients, 69.6 % (409/588) achieved SVR, 14.3 % (84/588) suffered relapse and 16.1 % (95/588) showed non-response. In a multivariate analysis, genotypes 2 or 3 and low age at treatment start were independent predictors of SVR. A total of 85.4 % of patients aged ≤ 40 years with genotype 2 or 3 had SVR.

INTERPRETATION We found good results for treatment of young patients with genotype 2 or 3 with pegylated interferon and ribavirin. Low age and viral genotype were predictors of sustained virologic response (SVR).

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MAIN POINTS

Treatment of chronic hepatitis C with pegylated interferon and ribavirin has been very effective in patients aged 40 or younger with genotypes 2 and 3.

Although new, effective antiviral drugs are available, we believe that pegylated interferon and ribavirin still have a place in the treatment of chronic hepatitis C genotypes 2 and 3.

Hepatitis C virus is a hepatotropic RNA virus that is transmitted through percutaneous exposure to blood, and in about 70 % of cases leads to chronic hepatitis. There are seven main variants of the virus, which are called genotypes 1–7 (1). Some 20 000 persons in Norway have a chronic hepatitis C infection. The prevalence among injection drug users is particularly high, with a prevalence of well over 50 % (2).

Hepatitis C is called «the silent epidemic». Very few individuals have symptoms before the infection has lasted for 30 years. One of three will develop cirrhosis of the liver and be at risk of liver failure and hepatocellular carcinoma (3). In a Norwegian cohort of opiate dependents who were infected with hepatitis C virus in the 1970s, liver disease was the primary cause of death after the age of 50 (4).

In the period 2000–2011, chronic hepatitis C was treated, in line with national and international guidelines, with a combination of pegylated interferon and ribavirin (5, 6). Interferon exerts an immunomodulatory effect by regulating interferon-stimulated genes, while the mechanism of ribavirin is unknown. This treatment has resulted in SVR in 40–80 % of the patients in international datasets (7, 8). The most important predictor of response to treatment has been the virus genotype, where genotype 2 responds better than genotype 3, which in turn responds better than genotype 1. Approximately 50 % of all cases of hepatitis C infections in Norway are caused by genotype 3. Genotype 1 occurs in about 40 % of cases, genotype 2 in about 10 %, while genotypes 4, 5 and 6 are only identified sporadically. Genotype 7 was recently detected in Africa and was not tested for in the period in question (1). We have limited data from Scandinavia on the effect of hepatitis C virus treatment administered in ordinary clinical practice (9, 10).

The world is now on the brink of an important change in the treatment of this condition. A number of new, direct-acting antiviral drugs have been launched and more are still under development. These drugs have yielded very good results in studies (11, 12), particularly for genotype 1. Pegylated interferon and ribavirin have been relatively expensive, and new anti-viral drugs will further increase treatment costs. In order to evaluate the additional value of new treatment against the increased costs, we need to know the results of the treatment we have administered up to now. Does the combination pegylated interferon and ribavirin still have a place in the treatment of hepatitis C?

The purpose of this study was therefore to evaluate the treatment response in patients with hepatitis C virus treated with pegylated interferon and ribavirin in ordinary clinical practice. We also wanted to identify factors associated with SVR, and to compare results and practice at different Norwegian hospitals.

Material and method

Criteria for inclusion

We included in this retrospective study HCV-RNA-positive, consecutive, treatment-naive patients at Stavanger University Hospital,

Table 1 Treatment-naive patients treated for hepatitis C with pegylated interferon and ribavirin in the period 2000–2011

	Total	Stavanger University Hospital	Akershus University Hospital	Østfold Hospital
Patients, number (%)	588 (100)	308 (52.4)	185 (31.5)	95 (16.2)
Age, years, average (SD)	39.6 (10.3)	37.2 (10.0)	43.1 (10.3)	40.4 (9.5)
Gender, number (%)				
Men	387 (65.8)	194 (62.7)	119 (64.3)	74 (77.9)
Women	201 (34.2)	114 (37.3)	66 (35.7)	21 (22.1)
Infection source, number (%)				
Intravenous abuse	401 (68.2)	222 (72.1)	112 (60.5)	67 (70.5)
Transfusion	32 (5.4)	17 (5.5)		5 (5.2)
Sexual contact	32 (5.4)	23 (7.5)	10 (5.4)	9 (9.5)
Unknown/other	123 (21)	46 (15)	63 (34.1)	14 (14.8)
Ethnic origin, number (%)				
European	419 (85.0)	269 (87.3)	150 (81.1)	Not available
Non-European	74 (15.0)	39 (12.7)	35 (18.9)	Not available
Ongoing intravenous abuse, number (%)	49 (8.3)	36 (11.7)	13 (7.0)	Not available
Treated with opioid replacement therapy, number (%)	59 (10.0)	43 (14.0)	9 (4.9)	7 (7.4)

Akershus University Hospital and Østfold Hospital who received at least one dose of pegylated interferon in combination with ribavirin in the period 2000–2011.

Data collection

At all three hospitals, patients treated for hepatitis C were registered consecutively in local quality registers with their person identification number. Relevant patients were identified by means of these registers, and clinical data were obtained retrospectively from electronic patient records. All patients who had received at least one injection with pegylated interferon were included in the study. The register at Østfold Hospital was based on data from the hospital in Sarpsborg, and therefore did not represent all treatments conducted at the hospital. Some patients had taken part in researcher-initiated phase 4 studies (13, 14). These patients were not excluded from the analyses, as the treatment they received (14 compared with 24 weeks of treatment for some patients with genotypes 2 and 3) did not differ from what in time has become standard treatment in Norway.

The following data were registered retrospectively at all hospitals: medication administration, treatment duration, HCV-RNA status week 4, status on termination of treatment and 24 weeks after treatment, genotype, viral load (low < 600 000 IU/ml, high > 600 000 IU/ml), sex, age and infection source. At Akershus and Stavanger university hospitals, levels of aspartate aminotransferase (AST) and platelets were recorded. This made it possible to calculate the APRI score (AST to platelet ratio index), which is a good non-invasive marker of advanced liver fibrosis (15). An APRI score of > 2 in the analyses was regarded as indicating the presence of cirrhosis.

Treatment

The standard treatment during the period was subcutaneously administered pegylated interferon-α-2a (Pegasys) 180 µg/week or pegylated interferon-α-2b (PegIntron) 1.5 µg/kg/week combined with ribavirin in tablet form. The great majority received a weight-based ribavirin dose (800–1400 mg/day), but some genotype 2 and 3 patients received 800 mg/day, in line with guidelines, irrespective of their weight.

The standard duration of treatment was 24 weeks for patients with genotype 2 or 3, and 48 weeks for genotype 1. Since 2008, the Norwegian guidelines (16) have allowed a treatment duration of only 14 weeks for genotype 2 or 3, and 24 weeks for genotype 1 in patients who were free of the virus in week 4 already (rapid virologic response – RVR). Patients who had not achieved a 2 log fall in viral load by week 12 were classified as non-responders. The treatment of these patients was terminated in accordance with the guidelines. Patients who had discontinued their treatment or had not had their HCV-RNA status analysed 24 weeks after the termination of treatment were also classified as non-responders. Relapse was defined as being HVC-RNA negative during treatment, but reverting to positive after the termination of treatment.

Virus analysis

The methodology for qualitative and quantitative virus detection changed several times during the study period. Up until 2003, all such workup was done by the Norwegian Institute of Public Health using polymerase chain reaction test (PCR) amplification of viral RNA with a lower detection limit of 100 IU/ml. After 2003, virus workup was conducted locally. Qualitative HCV-RNA analysis was carried out using a Cobas Amplicor HCV monitor test, version 2.0, Roche with a lower detection limit of about 50 IU/ml, while viral load was measured

Table 2 Virus characteristics and degree of fibrosis among treatment-naive patients treated for hepatitis C with pegylated interferon and ribavirin in the period 2000–2011

	Total	Stavanger University Hospital	Akershus University Hospital	Østfold Hospital
Genotype, number (%)				
1	205 (34.8)	121 (39.4)	50 (27.0)	34 (35.8)
2	51 (8.7)	20 (6.5)	20 (10.8)	11 (11.6)
3	318 (54.1)	160 (51.9)	110 (59.6)	48 (50.5)
Others	11 (1.9)	5 (1.6)	4 (2.1)	2 (2.1)
Not available	3 (0.5)	2 (0.6)	1 (0.5)	0 0
Viral load, number (%)				
< 600 000 IU/ml	225 (38.3)	129 (41.9)	51 (27.6)	45 (47.4)
> 600 000 IU/ml	268 (45.5)	130 (42.2)	90 (48.6)	48 (50.5)
Unknown	95 (16.2)	49 (15.9)	44 (23.8)	2 (2.1)
Degree of fibrosis[1], number (%)				
Not cirrhosis	399 (67.9)	252 (81.8)	147 (79.4)	Not available
Cirrhosis	69 (11.7)	35 (11.4)	34 (18.4)	Not available
Not available	120 (20.4)	21 (6.8)	4 (2.2)	95 (100)
Supplementary infection, number (%)				
Hepatitis B (HBsAg+)	9 (1.5)	3 (1.0)	6 (3.2)	1 (1.1)
HIV	5 (0.9)	3 (1.0)	2 (1.1)	0 0

[1] Cirrhosis is diagnosed by an APRI score of > 2

with Cobas Taqman HCV test, Roche. Virus genotype was determined by the Norwegian Institute of Public Health or Oslo University Hospital, Ullevål using hybridisation technology (Inno-Lipa HCV, Fujirebio).

Endpoint

The primary endpoint of SVR is defined as non-detectable HCV-RNA in serum six months after the conclusion of treatment.

Statistics

Uni- and multivariate logistic regression analysis were carried out with SVR as a dependent variable. Age, sex, source of infection, treatment centre, viral load, APRI score, genotype, participation in opioid replacement therapy (ORT) and treatment period were selected as independent variables. Corrected and non-corrected odds ratio (OR) and 95 % confidence interval were calculated for the various predictors, with 0.05 as level of significance. Statistical calculations were carried out using IBM's SPSS version 21 (IBM, Armonk, NY, USA).

Ethical considerations

The project was assessed by the Regional Committee for Medical and Health Research Ethics (REC West), which concluded that reporting was not required. In accordance with guidelines, the project was reported to and approved by the Data Protection Office at the hospitals in question (references: Stavanger University Hospital: 2012/10, Østfold Hospital: 24860/3, Akershus University Hospital: 12–065).

Results

The study included 588 patients who were treated for the first time with the combination of pegylated interferon and ribavirin. The average age at the start of treatment was 39.6 years, and men accounted for 65.8 % of the population (Table 1). The dominant source of infection was intravenous abuse (68.2 %). Hepatitis C virus genotype 1 was found in 34.8 %, genotype 2 in 8.7 %, genotype 3 in 54.1 % and genotypes 4 and 6 together totalled 1.9 %. No patients were found to have genotype 5 (Table 2).

SVR was achieved in 409 patients (69.6 %), 84 (14.3 %) suffered relapse and 95 (16.1 %) were non-responders. In the category non-responders, 52 patients were real non-responders, the remaining 43 had discontinued treatment for various reasons.

Treatment results by genotype

Genotype 1. SVR was achieved in 57.6 % (118/205) patients with genotype 1 (Fig. 1). RVR (data from Stavanger University Hospital and Akershus University Hospital) was achieved in 38/120 (32 %). Of the 38 patients with RVR, 37 achieved SVR (97 %). In this group, 28/38 received short-term treatment (24 weeks), and 27 (96 %) of these 28 achieved SVR. Of the group of patients with a low viral load before treatment, 69 % achieved SVR, while the figure for the group with a high viral load was 51 %. Data for SVR at the different centres are presented in Figure 2.

Genotype 2 and genotype 3. Of the patients with genotype 2, 78.4 % (40/51) achieved SVR, while the corresponding proportion for genotype 3 was 75.8 % (241/318)

(Fig. 1). RVR (data from Stavanger University Hospital and Akershus University Hospital) was shown by 81.8 % (27/33) with genotype 2 and 75 % (159/212) with genotype 3. Of those with RVR, SVR was achieved in 86.4 % with genotype 2 and 86.5 % with genotype 3. In the categories low and high viral load, 80 % and 72 %, respectively, achieved SVR (analysed collectively because of few genotype 2 patients). Of 186 patients with genotype 2 or 3 and RVR, 136 received short-duration treatment (12–16 weeks), and SVR was achieved in 84.6 % of cases. Irrespective of RVR and length of treatment, 85.4 % of patients aged ≤ 40 with genotype 2 or 3 had SVR.

Factors associated with response to treatment

Using logistic regression analysis and a multivariate model, we found that SVR was associated with age and genotype (Table 3).

Figure 3 shows the effect of age on SVR for genotypes 2 and 3. The degree of fibrosis was not included in our main regression model owing to a lack of data from Østfold Hospital. However, we performed a multivariate analysis on data from Stavanger University Hospital and Akershus University Hospital with age, genotype and APRI score as predictors for SVR. The analysis revealed a possible negative effect on SVR due to cirrhosis (OR = 0.6 CI 0.3–1.02, p = 0.06). This analysis showed almost the same results for the predictors age and genotype as the data presented in Table 3.

Opioid replacement therapy

We registered 59 patients who were receiving treatment for hepatitis C infection during ongoing opioid replacement therapy (ORT). An analysis of response to treatment revealed SVR of 47.4 % for genotype 1 and 87.5 % for genotypes 2 and 3. The incidence of discontinued therapy was not higher in this group. The regression analysis (Table 3) revealed no increased risk of patients in opioid replacement therapy discontinuing their hepatitis therapy.

Reasons for discontinued therapy

Electronic patient records at Stavanger University Hospital were studied closely to reveal the reasons for discontinuing therapy. In 88.9 % (274 of 308) cases, the therapy was completed according to the original plan. A total of 13 of 308 (4.2 %) of treatments were discontinued because of adverse reactions and 11 (3.6 %) of discontinuations were related to viral breakthrough, often because of noncompliance. Five treatments (1.6 %) were discontiued for unknown reasons, while three patients (1 %) discontinued treatment because of active drug abuse and two (0.6 %) due to intercurrent illness.

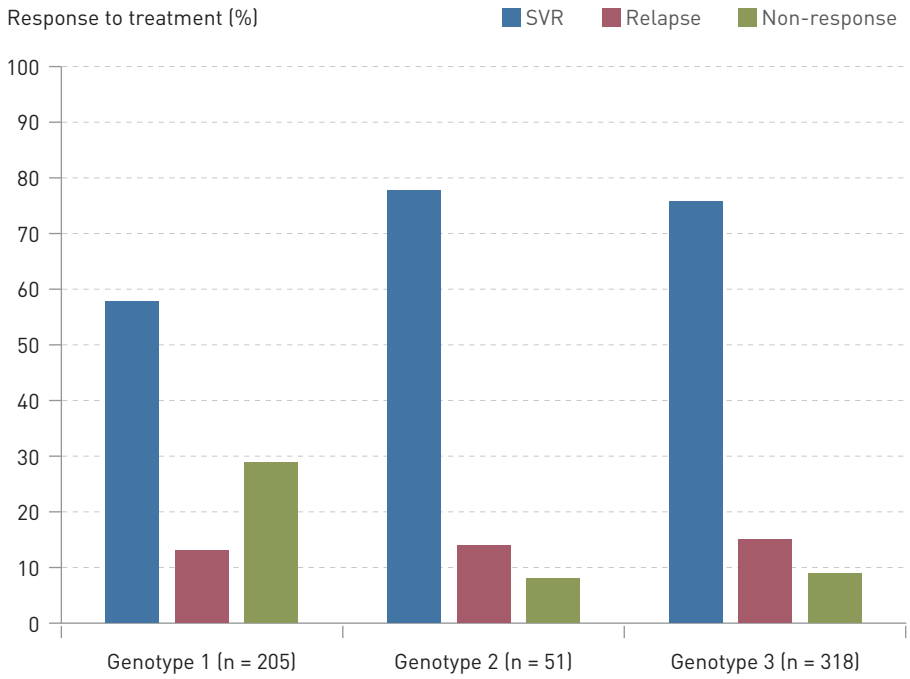

Figure 1 *Hepatitis C treatment with pegylated interferon and ribavirin. Treatment response in per cent, by genotype. The total of responses per genotype amounts to 100 %. Patient numbers are given in brackets*

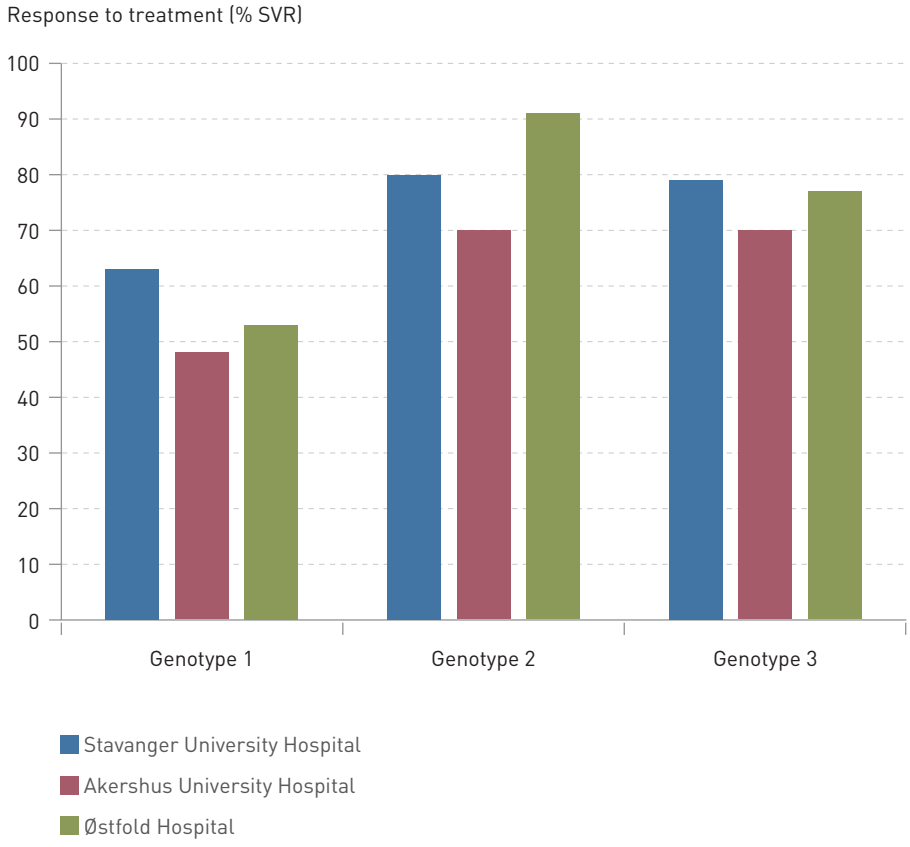

Figure 2 *Hepatitis C treatment with pegylated interferon and ribavirin. Percentage of treatments that have resulted in sustained virologic response, broken down by genotype and hospital providing treatment*

Table 3 Multivariate analysis of predictors for SVR following hepatitis C treatment with pegylated interferon and ribavirin

Predictor		Odds ratio (95 % CI) Non-corrected	Odds ratio (95 % CI) Corrected
Gender	Men	1	
	Women	1.16 (0.80 – 1.69)	
Age at treatment start	≤ 30 years	1	1
	31 – 40	0.48 (0.26 – 0.90)[1]	0.55 (0.29 – 1.03)
	41 – 50	0.21 (0.12 – 0.39)[1]	0.23 (0.10 – 0.43)[1]
	> 50	0.15 (0.08 – 0.29)[1]	0.17 (0.08 – 0.35)[1]
Infection source	Intravenous substance abuse	1	
	Other infection sources	0.93 (0.64 – 1.35)	
Genotype	1	1	1
	2	2.68 (1.30 – 5.52)[1]	3.58 (1.67 – 7.69)[1]
	3	2.31 (1.58 – 3.37)[1]	2.24 (1.50 – 3.35)[1]
Treatment centre	Stavanger University Hospital	1	1
	Akershus University Hospital	0.66 (0.45 – 0.98)[1]	0.82 (0.53 – 1.14)
	Østfold Hospital	0.90 (0.54 – 1.49)	1.0 (0.57 – 1.73)
Viral load	< 600 000 IU/ml	1	1
	> 600 000 IU/ml	0.56 (0.38 – 0.83)[1]	0.67 (0.44 – 1.03)
Opioid replacement therapy	Not treated	1	
	Treated	1.31 (0.71 – 2.43)	
Treatment period	2000 – 2006	1	
	2007 – 2011	1.18 (0.83 – 1.68)	

[1] $p < 0.05$ The predictors that had a p-value of < 0.1 in the univariate model were included in the multivariate regression model.

Discussion

In this retrospective analysis of hepatitis C therapy in ordinary clinical practice at three Norwegian hospitals, we found that 70 % of the patients achieved SVR after combination treatment with pegylated interferon and ribavirin. Response to treatment was strongly correlated with the patient's age: the later in life treatment was administered, the more difficult it was to achieve SVR.

This is the largest Scandinavian study of the effect of hepatitis C treatment. It shows good results for treatment compared with other reports from clinical practice. A large Danish dataset from 2011 showed SVR rates for genotypes 1, 2 and 3 infection of 44 %, 74 % and 71 %, respectively (9). The corresponding figures for our dataset were 57 %, 77 % and 78 %. A smaller dataset from Haukeland University Hospital yielded SVR rates of 44 % for genotype 1 and 75 % for genotype 3 (only two with genotype 2) (10). By way of comparison, an Australian prospective multicentre study from 2012 referred to a sustained virological response rate of 50 % for genotype 1 and of 70 % for genotypes 2 and 3 (17). Corresponding figures from a French retrospective study were 34 %, 58 % and 52 % for genotypes 1, 2 and 3, respectively, analysed according to an intent-to-treat protocol (18). By way of comparison, past approval studies have shown 46–52 % SVR for genotype 1 and 76–84 % for genotypes 2 or 3 (7, 8).

Our data show that the older the patient, the more difficult it is to achieve SVR with interferon-based therapy. We found 83 % lower SVR, irrespective of genotype, in patients over the age of 50 than in patients who were treated before the age of 30. With genotypes 2 and 3, SVR fell from 91 % in patients aged 30 or less to 61 % in those over 50.

We believe that the high percentage of patients in our dataset who achieve SVR is due to the fact that the patients were younger than those treated in other countries. The median age at the start of treatment was 46 in the Danish population, while the median age at the start of treatment was 39 in our study. Increasing age in itself results in reduced sensitivity to interferon. In addition the degree of fibrosis increases with age, and will contribute to lower SVR rates (14, 19).

In our study there are quite large variations in the rates of SVR between the Norwegian hospitals. The rate was 63 % for genotype 1 at Stavanger University Hospital compared with 48 % at Akershus University Hospital. Similarly, the average age at the start of treatment for patients with genotype 1 was 38 and 45, respectively, for the two populations. After correcting for age, we found no difference in response to treatment between the hospitals.

Whereas it has been the general consensus that all patients with genotypes 2 or 3 should receive treatment, there has been less consensus on the indication for treatment of patients with genotype 1 (16). Because the course of hepatitis C is benign in many, and

the adverse reactions associated with 48 weeks of pegylated interferon are substantial, the doctors at Akershus University Hospital have generally elected to watch and wait, and only treated those with severe liver fibrosis and/or substantial inflammation. The choice made at Stavanger University Hospital and Østfold Hospital has often been to treat everyone who is motivated, because young people with little liver damage respond better to treatment.

Still a part to play?

New, direct-acting antiviral drugs are less effective with genotype 3 infections than with other genotypes. One study compared pegylated interferon and ribavirin for 24 weeks with a combination of the direct-acting drug sofosbuvir and ribavirin for 12 weeks in treatment-naive patients with genotypes 2 and 3 (11). The authors presented good results for genotype 2, with a SVR rate of 97 %, but with genotype 3 the rate was under 60 %. When the length of treatment with sofosbuvir and ribavirin was extended to 24 weeks, the results were substantially better, with 93 % SVR (12). Sofosbuvir and ribavirin are better tolerated than pegylated interferon and ribavirin, but there is a large price difference for the two regimes: twenty four weeks of sofosbuvir and ribavirin cost about NOK 897 000 (20) while 12 weeks of pegylated interferon and ribavirin cost about NOK 33 000 (21, 22).

The great majority of young patients with genotype 2 or 3 will achieve a RVR, and thus have an up to 90 % probability of achieving SVR after only 12–16 weeks of treatment with pegylated interferon and ribavirin. The Norwegian Medical Association's guidelines on hepatitis C treatment (23) recommends trying pegylated interferon and ribavirin on patients aged ≤ 40 with genotypes 2 and 3. Our findings provide support for this recommendation.

Methodological weaknesses

The retrospective design of the study allows several sources of error. We cannot exclude a certain degree of selection bias. Patient inclusion may be incomplete; complete inclusion depends on the individual hospital registers not having deficiencies. At Stavanger University Hospital, control searches were conducted in electronic patient records after a review of the hepatitis C register. Consistency was found to be good, with few omitted patients. This was not done at Akershus University Hospital or Østfold Hospital.

The variables were chosen retrospectively, after the treatments had been administered. As a result some data, such as degree of fibrosis and ethnicity, are not available from all hospitals.

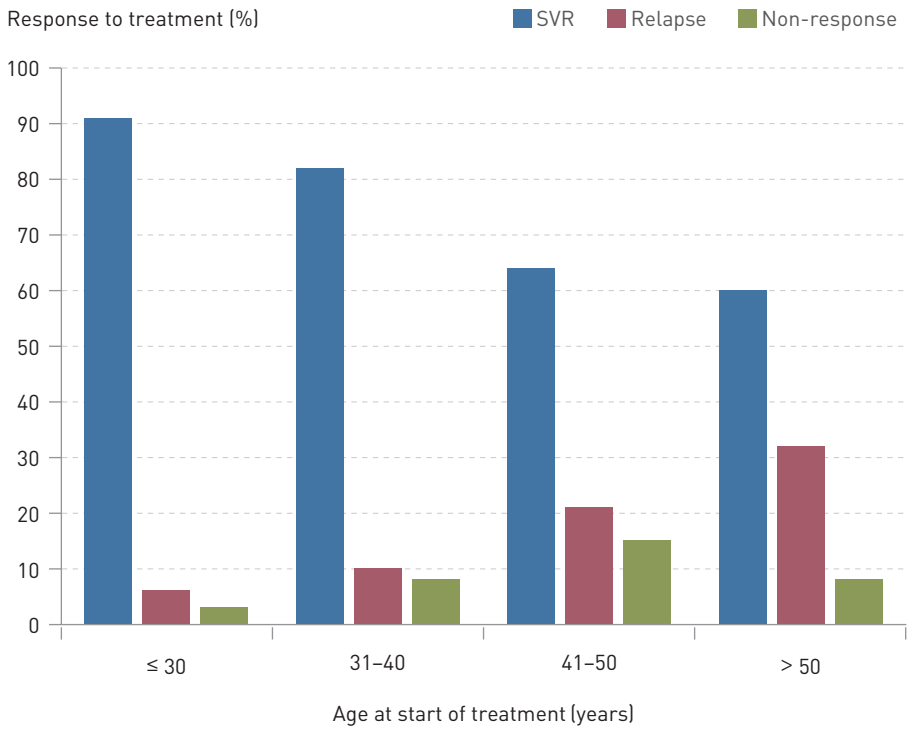

Figure 3 *Hepatitis C treatment with pegylated interferon and ribavirin. The figure shows treatment response in per cent for genotypes 2 and 3 broken down by age at treatment start. The total of responses per age category amounts to 100 %*

Conclusion

We concluded that the possibility of achieving SVR after treatment with pegylated interferon and ribavirin at Norwegian hospitals, irrespective of genotype, is 70 %. Age at the start of treatment was important as well as genotype, a known predictor of treatment success.

We have achieved especially good results in clinical practice with short-duration treatment using pegylated interferon and ribavirin for genotypes 2 and 3 in younger patients. The additional benefit of using direct-acting antiviral drugs would probably be limited in this population.

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