Treatment outcomes in a centralized specialty clinic for hepatitis C virus are comparable with those from clinical trials

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BACKGROUND: Outcomes from industry-sponsored registration trials are often considered to be more favourable than those achieved in clinical practice because patients involved in the former are highly selected and supported, but it is not known if this impression is valid.
OBJECTIVE: To determine the outcome of hepatitis C virus (HCV)-infected patients who received therapies for chronic HCV in a single urban centre and compare the results with those derived from contemporary, industry-sponsored trials.
DESIGN: Retrospective chart review of HCV-infected patients referred to the Viral Hepatitis Investigative Unit in Winnipeg, Manitoba, between 1998 and 2003.
METHODS: The Viral Hepatitis Investigative Unit database was used to identify all referred patients with positive anti-HCV antibodies. Charts were reviewed for the following data: patient demographics; viral genotype; indications and contraindications to treatment; treatment type; and outcome of antiviral therapy.
RESULTS: For 1800 anti-HCV positive patients identified, 1078 charts were available for review. Of these patients, the mean age was 47 years (range 11 years to 90 years) and 53% were men. Genotype 1 was the most common (65%). A total of 331 patients (31%) had received antiviral therapy. The sustained viral responses were similar to those described in industry-sponsored registration trials. Specifically, the sustained viral responses for interferon-alpha monotherapy (n=81) was 22.2%, interferon-alpha plus ribavirin (n=180) 44.4%, pegylated interferon monotherapy (n=38) 44.7% and pegylated interferon plus ribavirin (n=24) 54.2%.
CONCLUSION: HCV treatment outcomes from a single urban centre were similar to those described in industry-sponsored registration trials despite the high selection and support provided to patients enrolled in the latter studies.

Key Words: *Hepatitis C; Hepatitis C virus; HCV therapy; Outcomes*

Les issues des traitements dans une clinique de spécialité centralisée

HISTORIQUE : Les issues d'essais d'homologation commandités par l'industrie sont souvent considérées plus favorables que celles d'essais réalisés en pratique clinique parce que les patients qui participent aux premiers sont hautement sélectionnés et soutenus. On ne sait toutefois pas si cette impression est valide.
OBJECTIF : Déterminer l'issue des patients infectés par le virus de l'hépatite C (VHC) qui ont reçu des traitements pour le VHC chronique dans un seul centre urbain et comparer les résultats avec ceux dérivés d'essais contemporains commandités par l'industrie.
CONCEPTION : Analyse rétrospective de dossiers de patients infectés par le VHC aiguillés vers la *Viral Hepatitis Investigative Unit* de Winnipeg, au Manitoba, entre 1998 et 2003.
MÉTHODOLOGIE : La base de données de la *Viral Hepatitis Investigative Unit* a été utilisée pour repérer tous les patients aiguillés à cause d'anticorps anti-VHC positifs. Les dossiers ont été analysés pour en tirer les données suivantes : démographie des patients, génotype viral, indications et contre-indications de traitement, type de traitement et issue de la thérapie antivirale.
RÉSULTATS : Des 1 800 patients positifs aux anticorps anti-VHC repérés, 1 078 dossiers étaient disponibles pour l'analyse. Ces patients étaient d'un âge moyen de 47 ans (fourchette de 11 à 90 ans), dont 53 % d'hommes. Le génotype 1 était le génotype principal (65 %). Au total, 331 patients (31 %) avaient reçu une thérapie antivirale. Les réponses virales soutenues étaient similaires à celles décrites dans les essais d'homologation commandités par l'industrie. Plus précisément, les réponses virales soutenues à la monothérapie à l'interféron alfa (n=81) étaient de 22,2 %, à l'interféron alfa associé à la ribavirine (n=180), de 44,4 %, à la monothérapie à l'interféron pégylé (n=38), de 44,7 %, et à l'interféron pégylé associé à la ribavirine (n=24), de 54,2 %.
CONCLUSION : Les issues du traitement du VHC dans un seul centre urbain étaient similaires à celles décrites dans des essais d'homologation commandités par l'industrie, malgré la sélection et l'appui importants fournis aux patients qui participent à ces essais d'homologation.

Hepatitis C virus (HCV) infection is the leading indication for liver transplantation in Canada (1). It has been estimated that 0.8% or 240,000 Canadians are infected with HCV (2,3). Without effective treatment, the prevalence of cirrhosis due to HCV is expected to increase by 92%, liver failure by 126%, hepatocellular carcinoma by 102% and deaths associated with HCV by 126% before 2008 (3). Similar predictions have been described in France, the United States and elsewhere (4-6).

On the basis of the results of registration trials, treatment with recombinant interferon-alpha (r-IFNα) alone results in a sustained virological response (SVR) rate of 20% to 25%, r-IFNα plus ribavirin results in 39% to 41% and pegylated IFNα plus ribavirin results in 54% to 56% (7-13). By necessity, however, these trials invoked extensive inclusion and exclusion criteria, which raised concerns regarding their applicability to the general HCV patient population. Moreover, the

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TABLE 1
Contraindications for therapy

Contraindication	n	%
Mild histological disease	181	24.2
Hepatitis C RNA-negative	138	18.5
Normal alanine aminotransferase	84	11.2
Active alcohol use	57	7.6
Active psychiatric problems	56	7.5
Patient choice	39	5.2
Active drug use	35	4.7
Considering treatment	31	4.1
Other liver disease	20	2.7
Waiting for biopsy	16	2.1
Cardiac disease	11	1.5
Medical compliance issues	9	1.2
Seizure disorder	5	0.7
Cancer	5	0.7
Decompensated liver disease	3	0.4
Autoimmune disease	3	0.4
Severe anemia	3	0.4
Age	3	0.4
No reason documented	48	6.4
Total	747	100

provision of adequate nursing and support staff in such trials maximizes the likelihood of drug compliance and patient follow-up. Finally, the centres primarily involved in these trials are often of tertiary care, which can result in referral bias.

The intent of the present study was to compare the results of HCV treatments described in industry-sponsored registration trials (12,13) with those obtained in a single outpatient clinic serving greater than 90% of the catchment area. Given that the Viral Hepatitis Investigative Unit (VHIU, Health Sciences Centre, University of Manitoba, Winnipeg, Manitoba) is responsible for over 90% of patients affected by HCV in Manitoba, the data reflect all patients and as a result would not be influenced by referral bias to tertiary care centres. A secondary objective was to document the prevalence of contraindications to treatment and causes for discontinuing treatment once initiated.

METHODS

Patients referred to the VHIU between January 1998 and December 2003, with positive testing for anti-HCV by third generation enzyme immunoassay, were identified by the unit's computerized database. Charts from these patients were then accessed and reviewed for the following data: patient demographics; HCV genotype; indications and contraindications to treatment; type of treatment; and response to therapy. Decisions regarding treatment were based largely on the most recently published American Association for the Study of Liver Diseases (AASLD) (14) and Canadian Association for the Study of the Liver (CASL) (15) guidelines as interpreted by one of four attending VHIU hepatologists. Treatment if indicated was delivered by VHIU nurses in conjunction with the attending hepatologist. Patients were considered eligible for therapy if they met the AASLD or the CASL guidelines and there were absolutely no contraindications to the use of either IFN or ribavirin. While on therapy, all patients were followed up weekly for one month, every two weeks for two months and monthly thereafter. Post-treatment follow-up was offered at three and six months.

TABLE 2
Reasons for discontinuation of treatment

Reason	n	%
Severe side effects	20	45.5
Psychiatric	12	27.3
Noncompliance	5	11.4
Cardiac problems	3	6.8
Substance abuse	2	4.6
Allergic reaction	2	4.6
Total	44	100

RESULTS

For 1800 anti-HCV positive patients identified, 1078 patient charts were available for review. The average age of these patients was 47 years (range 11 to 90 years) with a male to female ratio of 53% to 47%. The majority of patients were infected with genotype 1 (65%), 34% were infected with genotypes 2 or 3 and 1% with genotypes 4, 5 or 6.

Three hundred thirty-one patients (31%) were treated with the most recently licensed therapy available. Sixteen nonresponders or relapsers were treated on more than one occasion with newer therapies as they became available.

The indications for treatment were persistently elevated (1.5-fold) serum aminotransferase values and histological evidence of at least grade 2 inflammation with or without stage 2 fibrosis as defined by the consensus guidelines. The contraindications to therapy are outlined in Table 1. Mild histological disease as defined by a METAVIR fibrosis score of 0 or 1 (24.2%), negative HCV RNA (18.5%) and normal liver enzymes (11.2%) constituted the majority (53.9%) of contraindications. Two other common reasons were active alcohol abuse and active psychiatric problems. These reasons where in agreement with the consensus statements from both the AASLD and the CASL (16,17).

The reasons why therapy had to be discontinued are outlined in Table 2. Treatment was discontinued in 44 patients (13.3%). The most common reasons were severe constitutional side effects (flu-like illness) that prompted the patient to request that treatment be terminated.

The results obtained with the various therapies used are outlined in Table 3. The total number of treatments exceeded the total number of charts reviewed because 16 patients received more than one course of therapy. The majority of treatment courses (180) were r-IFNα plus ribavirin (51.9%) and the remainder were r-IFNα alone (23.3%), pegylated IFNα alone (11%) or pegylated IFNα plus ribavirin (6.9%). Of note, pegylated IFNα did not become the standard of care until May 2003 in Canada.

Of 81 treatment courses with r-IFNα monotherapy, 18 patients (22.2%) achieved an SVR, six patients (7.4%) relapsed after therapy and 47 patients (58%) were nonresponders.

Regarding 180 treatment courses of r-IFNα plus ribavirin, 80 patients (44.4%) achieved an SVR, 17 patients (9.4%) relapsed after therapy and 53 patients (29.4%) were nonresponders.

Regarding 38 treatment courses of pegylated-IFNα monotherapy, 17 patients (44.7%) achieved a SVR, five patients (13.2%) relapsed after therapy and 13 patients (34.2%) were nonresponders.

TABLE 3
Treatment outcomes

Treatment	Duration (months)	Total		SVR		Relapser		Nonresponder		Discontinued	
		n	%	n	%	n	%	n	%	n	%
IFN	3	20	5.8	1	1.2	0	0.0	16	19.8	3	3.7
	6	32	9.2	8	9.9	3	3.7	17	21.0	4	5.0
	12	29	8.4	9	11.1	3	3.7	14	17.3	3	3.7
	Total	81	23.3	18	22.2	6	7.4	47	58.0	10	12.3
IFN + RBV	3	41	11.8	1	0.6	3	1.7	15	8.3	22	12.2
	6	79	22.7	36	20.0	12	6.7	26	14.4	5	2.8
	12	60	17.3	43	23.9	2	1.1	12	6.7	3	1.7
	Total	180	51.9	80	44.4	17	9.4	53	29.4	30	16.7
P-IFN	3	4	1.2	0	0.0	0	0.0	3	7.9	1	2.6
	6	10	2.9	2	5.3	2	5.3	6	15.8	0	0.0
	12	24	6.9	15	39.4	3	7.9	4	10.6	2	5.3
	Total	38	11.0	17	44.7	5	13.2	13	34.2	3	7.9
P-IFN + RBV	3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	6	5	1.4	3	12.5	0	0.0	0	0.0	2	8.3
	12	19	5.5	10	41.7	5	20.8	4	16.7	0	0.0
	Total	24	6.9	13	54.2	5	20.8	4	16.7	2	8.3
Other	3	2	0.6	0	0.0	0	0.0	1	4.2	1	4.2
	6	10	2.9	3	12.5	5	20.8	2	8.3	0	0.0
	12	12	3.5	4	16.7	2	8.3	6	25.0	0	0.0
	Total	24	6.9	7	29.2	7	29.2	9	37.5	1	4.2
Total		347								46	13.3

IFN Interferon-alpha; Other Consensus IFN, beta IFN and maintenance IFN; P Pegylated; RBV Ribavirin; SVR Sustained virological response

Finally, of 24 treatment courses with pegylated IFNα plus ribavirin, 13 patients (54.2%) achieved an SVR, five patients (20.8%) relapsed after therapy and four patients (16.7%) were nonresponders.

DISCUSSION

The principal finding of the present study is that the results described from registration trials for IFN-based treatment of chronic HCV are similar to those obtained in unselected patients attending a single urban health care facility (8,9,18). The results also confirm the findings of a previous report (19) that only a minority of patients with chronic HCV are candidates for antiviral therapy.

The impression that registration trials tend to provide more favourable results than findings in clinical practice is based on a number of factors. First, registration trials are designed to limit the enrollment of patients with comorbidities that can conceivably interfere with drug or agent delivery or ascertainment of outcome measures. Second, participating sites in registration trials are supported such that adequate nursing and ancillary support staff are in place to optimize patient care and maximize patient monitoring and follow-up. Third, intuitively, well-defined protocols for dosage adjustments secondary to suboptimal responses or the appearance of side effects is more likely to be beneficial than the relatively ad hoc adjustments often made in clinical practice. Finally, ready access to third parties involved in registration trials with expertise in the area further enhances the quality of care that can be provided in the context of such trials.

Despite the above considerations, the SVR rates described in the present report were similar to those described in the relevant registration trials. The explanation for this finding remains to be determined. Of note, the study population described in the present study was comparable with those of registration trials in terms of the prevalence of those factors most often associated with responsiveness to IFN-based therapy such as patient age, sex, viral genotype and liver histology. Not documented in the present study or in certain registration trials were viral load, body mass index and the presence of fatty infiltration of the liver, which have also been used to predict outcome after treatment.

If confirmed in subsequent studies, the practical implication of this finding is that figures generated from registration trials and often quoted to patients for likelihood of successful treatment are largely applicable to community-based clinical practices. One likely proviso is that the community-based practice must include a trained hepatologist and nurses experienced in the care of patients with viral hepatitis.

In a similar sized single centre study reported by Falck-Ytter et al (19), only 28% (of 239 subjects) proceeded to treatment for chronic HCV. In that study, treatment was withheld in 37% of patients because they "did not adhere to evaluation procedures," in 34% because of medical or psychiatric contraindications, in 13% as a result of ongoing substance or alcohol abuse, in 11% because they refused treatment, in 10.4% who were HCV RNA-negative and in 5% because they had normal liver enzymes. Although the overall result (percentage of patients proceeding to treatment) was similar in the two studies (28% versus 31% in the present study), reasons for not treating differed. Specifically, in the present study, the most common obstacles to treatment were mild or normal liver histology (24.2%), negative HCV RNA testing (18.5%), ongoing substance or alcohol abuse (12.3%), normal liver enzyme concentrations (11.2%), active psychiatric problems (7.5%) and patient refusal (5.2%).

The present study has several limitations that require consideration. First, the retrospective study design renders it susceptible to all the limitations inherent in such studies. Second, although the VHIU where the data were generated reviews greater than 90% of HCV cases diagnosed in the catchment

area, and thereby decreases the risk of referral bias as the only HCV treatment centre in the area, referral bias cannot be totally eliminated. The period of evaluation ending in 2003 identified 1800 charts. During this same time period, the Cadham Provincial Laboratory of Manitoba (Winnipeg, Manitoba) had identified only just over 2000 patients confirming the minimal referral bias. Third, the absence of similar efficacy data from other sites renders it difficult to determine whether these findings are site specific.

In summary, HCV-infected patients can be treated within a clinic setting with expectations of similar results to those described in industry-sponsored registration trials. However, therapy remains limited to a relatively small minority of patients.

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