UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Département de médecine
Service des maladies infectieuses

« Role of Hepatitis C virus genotype 3 in liver fibrosis progression – a systematic review and meta-analysis »
et
« Impact of a nurse vaccination program on hepatitis B immunity in a Swiss HIV clinic »

THESE

préparée sous la direction du Docteur PD Pierre-Yves Bochud
(avec la co-direction du Professeur Thierry Clandra)

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Arnold PROBST

Médecin diplômé de la Confédération Suisse
Originaire de Berne

Lausanne

2012

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Ecole Doctorale
Doctorat en médecine

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Directeur de thèse	*Monsieur le Docteur* ***Pierre-Yves Bochud***
Co-Directeur de thèse	*Monsieur le Professeur* ***Thierry Calandra***
Expert	*Monsieur le Professeur* ***François Spertini***
Directrice de l'Ecole doctorale	*Madame le Professeur* ***Stephanie Clarke***

la Commission MD de l'Ecole doctorale autorise l'impression de la thèse de

Monsieur Arnold Probst

intitulée

Role of Hepatitis C virus genotype 3 in liver fibrosis progression - a systematic review and meta-analysis

&

Impact of a nurse vaccination program on hepatitis B immunity in a Swiss HIV clinic

Lausanne, le 18 octobre 2012

pour Le Doyen
de la Faculté de Biologie et de Médecine

Madame le Professeur Stephanie Clarke
Directrice de l'Ecole doctorale

Cette thèse est composée de deux articles qui font suite à une recherche relative aux virus de l'hépatite B et C, dont voici les résumés :

Rôle du génotype 3 du virus de l'hépatite C dans la progression de la fibrose hépatique, une revue systématique avec méta-analyse.

On estime à 170 millions le nombre de personnes atteintes d'hépatite C chronique dans le monde. La principale conséquence de cette maladie est la fibrose du foie, qui évolue plus ou moins rapidement, pour aboutir au développement d'une cirrhose et/ou d'un hépatocarcinome. Certains des facteurs accélérateurs de la fibrose, comme l'âge avancé au moment de l'infection, le sexe masculin, la consommation d'alcool, sont bien connus. On a longtemps considéré que les six différents génotypes viraux n'influençaient pas la progression de la fibrose. Des études récentes ont cependant suggéré que certains génotypes, en particulier le génotype 3, pouvaient entraîner une fibrose plus rapide.

Le but de ce travail de thèse était de déterminer à l'aide d'une méta-analyse le rôle du génotype viral dans la progression de la fibrose dans l'infection chronique au virus de l'hépatite C. Les études ont été sélectionnées dans la littérature médicale à partir d'une série de mots-clés. Le degré de fibrose a été estimé par biopsie, en utilisant le score Metavir. Deux types d'études ont décrits de manière différente la durée d'infection. Les premières ont calculé la progression de la fibrose depuis le moment estimée de l'infection (« études avec une biopsie »), les secondes ont exprimés cette durée comme étant l'intervalle entre deux biopsies (« études avec deux biopsies »).

L'analyse a permis d'identifier 8 études avec une biopsie pour un collectif total de 3182 patients ainsi que 8 études avec deux biopsies pour un collectif de 896 patients. Dans une méta-analyse de type « random effect », le rapport de cote pour l'association du génotype 3 avec une fibrose accélérée est de 1.52 (95% IC 1.12-2.07, p=0.007) pour les études à une biopsie. Pour les études à deux biopsies, le rapport de cote pour cette association est de 1.37 (95% IC 0.87-2.17, P=0.17).

Cette étude montre que les patients avec une hépatite C chronique due au génotype 3 ont une progression de fibrose plus rapide que ceux qui sont infectés par les autres génotypes. Alors que la méta-analyse des études avec une biopsie est clairement significative, celle des études avec deux biopsies est au-dessous du seuil de significativité. Les études à deux biopsies peuvent être limitées par plusieurs facteurs, comprenant un « biais d'indication » (seuls les patients évoluant rapidement vers la cirrhose ont plus de risque d'avoir une deuxième biopsie), une durée d'observation très courte (5 années comparée à 13 années pour les études à 2 biopsies), et un nombre de patient limité (896 pour le études à 2 biopsies comparé à 3182 pour les études à 1 biopsie).

Impact d'un programme de vaccination sur l'immunité contre l'hépatite B dans une clinique suisse du VIH

Le virus de l'hépatite B cause une infection aigüe dont la symptomatologie varie d'une présentation subclinique à une progression fulminante. Dans une minorité de cas, l'infection aigüe est suivie d'une infection chronique pouvant évoluer vers une cirrhose hépatique et/ou un hépatocarcinome. La prévalence de l'hépatite B aigüe et chronique chez les personnes vivant avec le virus d'immunodéficience humaine (VIH) est supérieure à celle de la population générale. Par ailleurs la co-infection avec le virus du VIH entraine une progression plus rapide de l'hépatite B. Dès lors, l'immunité pour le virus de l'hépatite B représente un facteur primordial de prévention dans la population infectée par le virus de l'HIV. Bien que l'administration d'un vaccin contre l'hépatite B soit particulièrement recommandée chez tous les individus infectés par le VIH, la couverture vaccinale dans cette population est souvent insuffisante.

Le but de cette étude était de déterminer l'état d'immunisation contre le virus de l'hépatite B dans la population infectée par le VIH de la cohorte Suisse HIV et d'analyser l'efficacité d'un programme de vaccination administré par le personnel soignant. L'immunité avant et après intervention dans notre centre a été comparée aux autres centres de la cohorte HIV en Suisse. L'immunité pour le centre d'intervention a passé de 32% avant intervention à 76% après intervention alors que pour les autres centres, l'immunité n'a progressé que de 33% à 39% dans le même laps de temps (n=2712, P=0.001). Cette étude montre qu'un contrôle systématique de l'immunité par du personnel soignant augmente de manière significative l'immunité pour le vaccin de l'hépatite B dans la population HIV.

JOURNAL OF VIRAL HEPATITIS JVH

Journal of Viral Hepatitis, 2011, **18**, 745–759 doi:10.1111/j.1365-2893.2011.01481.x

REVIEW

Role of Hepatitis C virus genotype 3 in liver fibrosis progression – a systematic review and meta-analysis

A. Probst,[1]* T. Dang,[2]* M. Bochud,[3] M. Egger,[4] F. Negro[5] and P.-Y. Bochud[1] [1]*Infectious Diseases Service, Department of Medicine, University Hospital and University of Lausanne, Lausanne, Switzerland;* [2]*Internal Medicine Service, Department of Medicine, University Hospital and University of Lausanne, Lausanne, Switzerland;* [3]*Institute for Social and Preventive Medicine, University Hospital and University of Lausanne, Lausanne, Switzerland;* [4]*Institute of Social and Preventive Medicine, Bern, Switzerland; and* [5]*Division of Gastroenterology and Hepatology, University Hospitals, Geneva, Switzerland*

Received February 2011; accepted for publication March 2011

SUMMARY. The progression of liver fibrosis in chronic hepatitis C has long been considered to be independent from viral genotypes. However, recent studies suggest an association between Hepatitis C virus (HCV) genotype 3 and accelerated liver disease progression. We completed a systematic review and meta-analysis of studies evaluating the association between HCV genotypes and fibrosis progression. PubMed, Embase and ISI Web of Knowledge databases were searched for cohort, cross-sectional and case–control studies on treatment-naïve HCV-infected adults in which liver fibrosis progression rate (FPR) was assessed by the ratio of fibrosis stage in one single biopsy to the duration of infection (single-biopsy studies) or from the change in fibrosis stage between two biopsies (paired biopsies studies). A random effect model was used to derive FPR among different HCV genotypes. Eight single-biopsy studies (3182 patients, mean/median duration of infection ranging from 9 to 21 years) and eight paired biopsies studies (mean interval between biopsies 2–12 years) met the selection criteria. The odds ratio for the association of genotype 3 with accelerated fibrosis progression was 1.52 (95% CI 1.12–2.07, $P = 0.007$) in single-biopsy studies and 1.37 (95% CI 0.87–2.17, $P = 0.17$) in paired biopsy studies. In conclusion, viral genotype 3 was associated with faster fibrosis progression in single-biopsy studies. This observation may have important consequences on the clinical management of genotype 3-infected patients. The association was not significant in paired biopsies studies, although the latter may be limited by important indication bias, short observation time and small sample size.

Keywords: fibrosis progression, genotype 3, hepatitis C, meta-analysis.

INTRODUCTION

The hepatitis C virus (HCV) chronically infects ~170 millions of persons worldwide, which represents ~3% of the world's population [1]. The important morbidity and mortality associated with chronic hepatitis C result mainly from the development of liver fibrosis and its evolution towards cirrhosis and hepatocarcinoma [2]. The identification of factors affecting fibrosis progression is critical for the optimal management of infected patients [3]. Factors associated with rapid progression include demographic characteristics (such as older age at infection and male sex), host genetic factors, viral co-infections (with the hepatitis B [HBV] or the human immunodeficiency virus [HIV]), metabolic features (such as steatosis, insulin resistance or iron overload) and exposure to toxic agents (alcohol, tobacco or cannabis) [4]. Risk factors identification for fibrosis progression was first based on fibrosis stage. However, this approach leads to significant bias, because disease duration varies widely across the population. This issue has been addressed, at least in part, by the estimation of fibrosis progression rate (FPR) based on the ratio of fibrosis stage to disease duration, which might better reflect the true fibrosis progression. Recent studies, using the latter method, suggested that some viral genotypes, such as genotype 3, are associated with more rapid fibrosis progression than other genotypes [5–7]. In this study, we

Abbreviations: DAA, direct antiviral agents; ES, effect size; FPR, fibrosis progression rate; HAI, histology activity index; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OR, odds ratio; RNA, ribonucleic acid.

Correspondence: Pierre-Yves Bochud, Infectious Diseases Service, Department of Medicine, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland. E-mail: pierre-yves.bochud@chuv.ch
*Equal contribution.

systematically reviewed the published literature about the impact of HCV genotypes on the natural history of chronic hepatitis C and conducted a meta-analysis of the studies reporting a FPR per genotype. Our aim was to examine the impact of viral genotype 3 on fibrosis progression compared with other genotypes.

MATERIAL AND METHODS

Search strategy

This meta-analysis was performed according to the PRISMA statement for reporting systematic reviews and meta-analyses [8]. Three electronic databases (PubMed, Embase and ISI Web of Knoweldge) were searched for published studies evaluating the fibrosis progression per genotype in chronic HCV before October 2009 (Table S1). Additionally, the investigators hand-searched the bibliographies of obtained articles and reviews; they did not contact any study authors for further information.

Eligible studies

Cohort, cross-sectional and case–control published trials studying the fibrosis progression in HCV-infected patients were eligible. There was no restriction on language or publication date. Participants were chronically infected with HCV genotype 3, and controls were chronically infected with other genotypes.

Study selection

Two investigators independently selected studies meeting the following criteria (Table S1): (i) chronic HCV infection; (ii) fibrosis scoring; (iii) no HCV treatment before biopsies; (iv) an estimated date of HCV infection; and (v) an estimated FPR per genotype. Studies on participants of <18 years of age, studies on orthotopic liver transplant recipients, studies without full text available and reviews were excluded. When more than one article was available from the same cohort, we included the article containing most complete information. Disagreements between the two investigators were solved by discussion.

Study quality assessment and data extraction

Quality criteria were reported for each study, including study design, case definition, liver biopsy quality, nonviral factors associated with fibrosis progression and method used to estimate the date of infection (Table S1). The two investigators independently extracted data for each study. The extracted data were then cross-checked by two other investigators for accuracy. FPR values were assessed together for all genotype non-3 patients. Patients with unknown genotype were not included.

Statistical analysis

Eligible studies were separated in two groups: those calculating FPR as the ratio of the fibrosis score to the interval between an estimated date of infection and one pretreatment liver biopsy (defined as 'single-biopsy studies') and those calculating fibrosis progression between two pretreatment liver biopsies ('paired-biopsies studies'). For single-biopsy studies, an effect size (ES) was calculated for each individual study (detailed in Appendix) [9]. ES of both continuous and dichotomous outcomes was pooled in the same meta-analysis using a random effect model [10]. ES was then transformed back to odds ratio (OR). For paired biopsies studies, the OR for comparison of genotype 3 *vs* others was calculated for each individual study. We performed a meta-analysis by pooling the OR using a random effect model. All statistical analyses were performed with Stata software (StataCorp, College Station, TX, USA), version 10.0.

RESULTS

From the 3133 citations yielded by the electronic database search, 2936 were excluded for nonrelevance after title or abstract screenings (Fig. 1). Among 197 remaining full-text papers, 181 were excluded for nonrelevance, inappropriate review design, use of post-treatment biopsy, lack of estimated HCV infection duration, or lack of data on genotyping (no data on genotype 3) or FPR. The remaining 16 studies (eight single-biopsy and eight paired biopsy studies) were selected for the meta-analysis. For single-biopsy studies in which both continuous and dichotomous outcomes were available [6,7], the continuous outcome was used.

The characteristics of the studies are shown in Table 1. In most studies, the primary endpoint was to assess together the role of several risk factors on fibrosis progression in chronically HCV-infected patients (N = 7 [6,7,11–15]). No study focused specifically on the role of viral genotypes, but some addressed specific factors such as steatosis (N = 5 [16–20]), cannabis use (N = 1 [5]), host genetic variants (N = 1 [21]), immunosuppression level in HIV-infected patients (N = 1 [22]) or transforming growth factor β (N = 1 [23]).

Overall, 3860 patients were included in the meta-analyses, 3182 (range 71–1157) from single-biopsy studies and 678 (range 20–136) from paired biopsies studies (Table S2). Most patients included in the studies were men (62%), the most frequent ethnicity was Caucasian (95%, data available in five studies) and the mean age was 42 years. The most frequent routes of infection were intravenous drug use (41%) and blood transfusion (31%). Eight studies included only HCV mono-infected patients (N = 8), two included both HCV mono-infected and HCV/HIV co-infected patients (percentage of co-infection 7% and 22%), two included only co-infected patients, while four other studies did not give any information on co-infection. The mean duration of HCV infection in single-biopsy studies was 13 years (range

Table 1 Quality assessment of studies on liver fibrosis progression with regard to hepatitis C virus genotype

Reference, year of publication	Country	Study design	Type of population and setting	Outcome	*N* liver biopsy per subject	Fibrosis scoring system	Biopsy quality (length of biopsy) and assessment (number of pathologist)	Population size, total	*N* with estimated duration of infection	Method used to assess date of infection	*N* with HCV genotyping	*N* with genotype 3 (%)	*N* genotype 3 with FPR or assessment of fibrosis progression
Poynard *et al.*, 1997 [11]	France	a. P b. R/P cohort c. R	a. Consecutive new patients biopsied in 1993 in 16 liver centres b. 1 liver centre c. Patients from five trials of interferon, with pre-treatment biopsy	FPR	1	METAVIR [24]	>10 mm	a. 1138 b. 607 c. 490	a. 703 b. 454 c. 0	No mention	a. unknown b. 323 c. 53	a. unknown b. 44 (14) c. 12 (23)	39
Shev *et al.*, 1997 [13]	Sweden	R	Patients with biopsy performed >9 years before inclusion in one tertiary hospital	Histological progression	2	Knodell HAI [26]	No mention: two blinded pathologists	20	–	–	20	6 (30)	6
Adinolfi *et al.*, 2001 [16]	Italy	P	Consecutive patients in one liver centre	Steatosis and FPR	1	Knodell HAI	No mention: one blinded pathologist	180	71	First reported event at risk	180	26 (14)	25

Table 1 (Continued)

Reference, year of publication	Country	Study design	Type of population and setting	Outcome	N liver biopsy per subject	Fibrosis scoring system	Biopsy quality (length of biopsy) and assessment (number of pathologist)	Population size. total	N with estimated duration of infection	Method used to assess date of infection	N with HCV genotyping	N with genotype 3 (%)	N genotype 3 with FPR or assessment of fibrosis progression
Kanzler *et al.*, 2001 [23]	Germany	R	Patients with ≥2 biopsies at an interval ≥12 months in tertiary centres	TGF-β and fibrosis progression	2	Ishak HAI [25] + Chevallier [40]	No mention: two blinded pathologists	39	–	–	39	3	3
Westin *et al.*, 2002 [18]	Sweden	R	One liver centre	FPR	2	Ishak HAI	No mention: two blinded hepatologists and one senior pathologist	78	–	–	74	22 (30)	22
Martinez-Sierra *et al.*, 2003 [12]	Spain	P case-control	One tertiary centre: Case: HIV-HCV co-infected patients Controls: HCV mono-infected patients	FPR	1	Desmet [27]	>10 mm: one blinded experienced pathologist	a. 41 b. 147	a. 41 b. 97	Questionnaire filled by patients	a. 41 b. 147	a. 14 (34) b. 38 (26)	a. 14 b. 38

Table 1 (Continued)

Reference, year of publication	Country	Study design	Type of population and setting	Outcome	*N* liver biopsy per subject	Fibrosis scoring system	Biopsy quality (length of biopsy) and assessment (number of pathologist)	Population size, total	*N* with estimated duration of infection	Method used to assess date of infection	*N* with HCV genotyping	*N* with genotype 3 (%)	*N* genotype 3 with FPR or assessment of fibrosis progression
Zarski *et al.*, 2003 [14]	France, USA	R	Consecutive patients in two French and three American tertiary centres	FPR	≥2	METAVIR	≥20 mm; one blinded pathologist	180	147	–	136	21 (15)	21
Fartoux *et al.*, 2005 [19]	France	R	One liver centre	Probability of fibrosis progression	2	METAVIR	≥10 mm; one blinded pathologist	135	135	–	135	22 (16)	22
Hézode *et al.*, 2005 [5]	France	P	Consecutive patients in one liver centre	FPR	1	METAVIR	No mention; one pathologist	270	270	First reported event at risk	267	66 (25)	66
Richardson *et al.*, 2005 [21]	Australia	P	One tertiary centre: a. Consecutive patients with pre-treatment biopsy b. Validation group of 24 liver transplant recipients	Host genetic polymorphisms and FPR	1	Scheuer [28]	No mention; one pathologist	a. 326	326	First reported event at risk	205	88 (43)	88

Table 1 (Continued)

Reference, year of publication	Country	Study design	Type of population and setting	Outcome	*N* liver biopsy per subject	Fibrosis scoring system	Biopsy quality (length of biopsy) and assessment (number of pathologist)	Population size, total	*N* with estimated duration of infection	Method used to assess date of infection	*N* with HCV genotyping	*N* with genotype 3 (%)	*N* genotype 3 with FPR or assessment of fibrosis progression
Perumalswami *et al.*, 2006 [20]	USA	R	1 tertiary centre: a. Treatment-naïve patients with one biopsy b. Subgroup with two biopsies	Steatosis and FPR	a. 1 b. 2	Ishak HAI	>10 portal tracts: one blinded pathologist	a. 494 b. 136	494	–	–	a. 23 (5)	b. 4
Bonnard *et al.*, 2007 [15]	France	R	HIV co-infected patients in one tertiary centre	FPR	2	METAVIR	≥10 mm: one blinded study pathologist, one experienced senior pathologist	32	30	–	29	7 (24)	7

Table 1 (Continued)

Reference, year of publication	Country	Study design	Type of population and setting	Outcome	*N* liver biopsy per subject	Fibrosis scoring system	Biopsy quality (length of biopsy) and assessment (number of pathologist)	Population size, total	*N* with estimated duration of infection	Method used to assess date of infection	*N* with HCV genotyping	*N* with genotype 3 (%)	*N* genotype 3 with FPR or assessment of fibrosis progression
Bochud *et al.*, 2009 [7]	Switzerland	P	Patients from a prospective cohort in eight tertiary centres and other affiliated local centres	FPR	1	METAVIR	No mention; unknown number of experienced pathologists	1189	1189	First reported event at risk	1130	316 (28)	316
Cross *et al.*, 2009 [17]	Great Britain	R	One tertiary centre	Steatosis and FPR	≥2	Ishak HAI	≥10 mm; one blinded pathologist	112	–	–	112	30 (27)	30
Hissar *et al.*, 2009 [6]	India	R	?	FPR	1	Knodell HAI	No mention; two blinded independent pathologists	213	213	First reported event at risk	140	105 (75)	105
Reiberger *et al.*, 2009 [22]	Austria	R	HIV co-infected patients in one tertiary centre	FPR	1	METAVIR	No mention; unknown number of experienced pathologists	74	74	First reported event at risk	74	24 (32)	24

P, prospective; R, retrospective; *N*, number; FPR, fibrosis progression rate; HAI, histology activity index; ALT, alanine transaminase; HIV, human immunodeficiency virus; TGF-β, transforming growth factor-β.

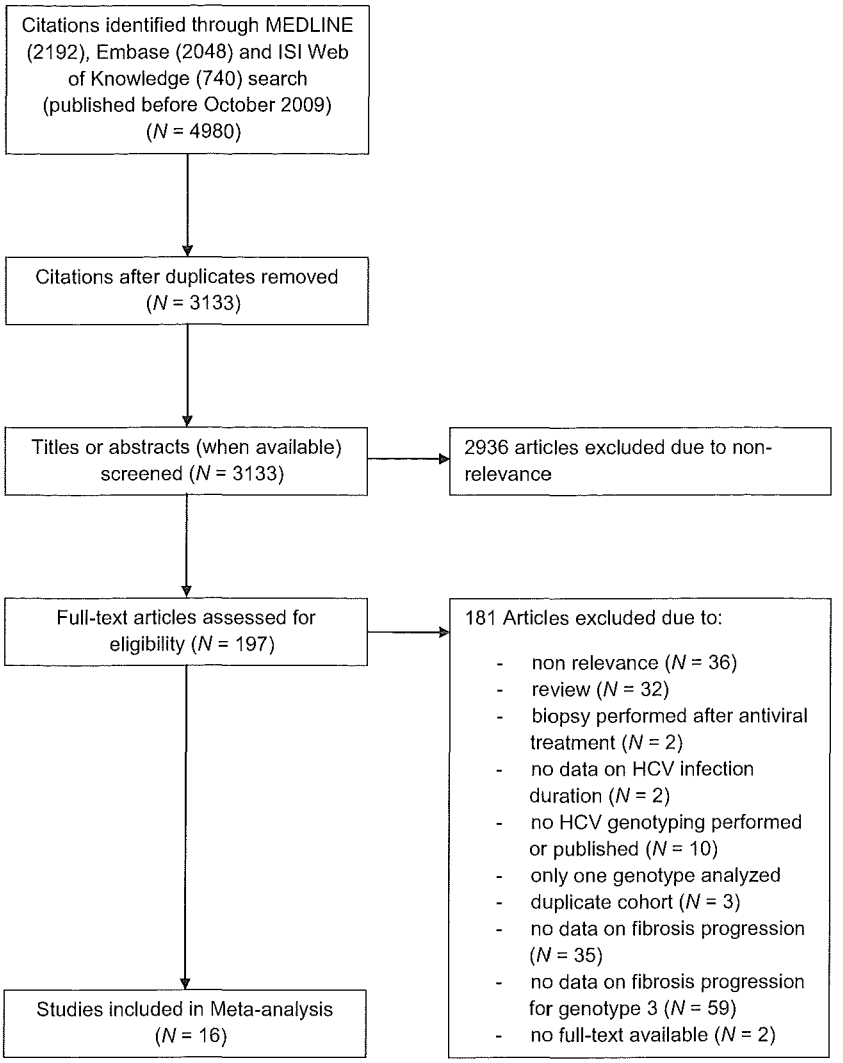

Fig. 1 Flow diagram for study selection.

10–17, six studies; median 9 and 21 years in two other studies). The mean interval time between paired biopsies was 5.3 years (range 2.3–12, 5 studies; median 4.1, 4.2 and 6 years in three other studies).

Study quality

The studies showed a relative homogeneity in terms of design and settings: 11 were retrospective cohort studies (Table 1), four were prospective cohort studies and one was a retrospective case–control study. All studies performed in tertiary hospitals or liver centres, and all published between 1997 and 2009 (Table 1). Seven studies gave a fibrosis score according to the METAVIR system [24], while four used Ishak's modified histology activity index (HAI) [25], three used the Knodell's HAI [26], one used Desmet's system [27] and one study gave Scheuer's grades [28] (scores summarized in Table S3). In most single-biopsy studies ($N = 6$), the date of infection was considered to be the first reported event at risk (blood transfusion, IV drug or nosocomial infection). In most studies, the association of viral genotype 3 with FPR was solely assessed in univariate models, with multivariate analyses performed in only three single-biopsy studies (Fig. S1).

Meta-analyses

The meta-analysis of single-biopsy studies showed a faster FPR in patients infected by genotype 3 compared with the others (overall pooled ES = 0.23, [95% CI 0.06–0.40], $P = 0.007$, OR = 1.52 [95% CI 1.12–2.07], Fig. 2). The I^2 test result was 62.2% ($P = 0.010$). Similar results were obtained when studies including HIV-infected patients were removed, but the number of patients was smaller ($N = 455$) and the association was at the limit of significance (OR = 1.67, [95% CI 0.99–2.85], $P = 0.056$). The cumulative meta-analysis showed that the effect of genotype 3 on fibrosis progression became significant only in 2009 (Fig. 3). The meta-analysis of paired biopsies studies showed a trend towards faster progression for genotype 3 patients compared

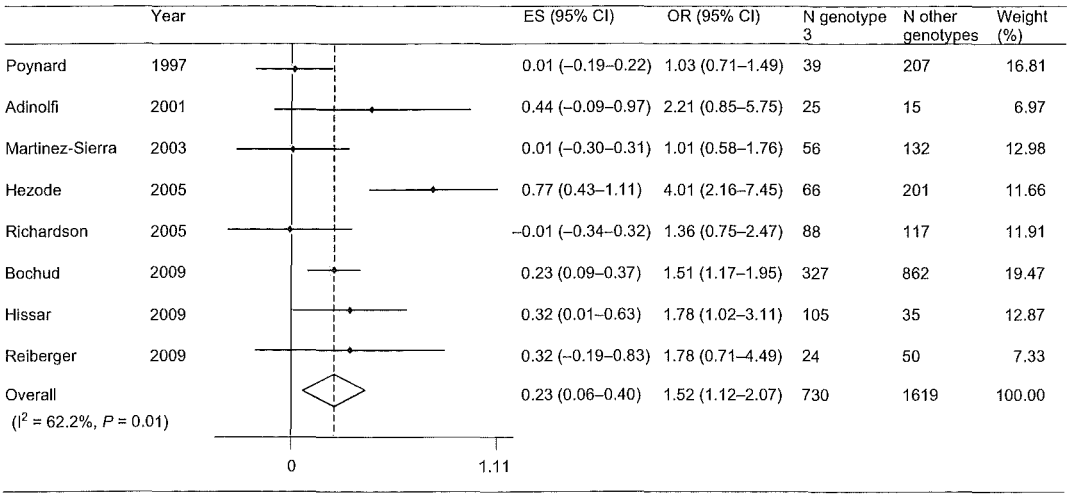

Fig. 2 Forest plot of fibrosis progression rates estimated from one biopsy, genotype 3 *vs* other genotypes. ES, effect size; OR, odds ratio; 95% CI, 95% confidence interval.

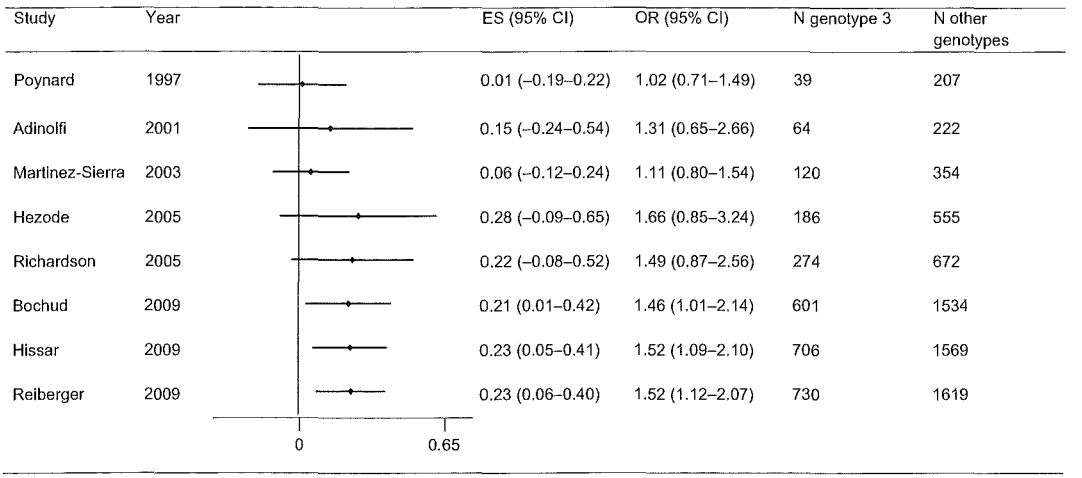

Fig. 3 Meta-cumulative analysis of studies estimating fibrosis progression rate based on an estimated date of infection, genotypes 3 *vs* non-3. ES, effect size; OR, odds ratio; 95% CI, 95% confidence interval.

with the others (OR = 1.37, 95% CI 0.87–2.17, P = 0.17, Fig. 4). The I^2 test was 0.0% (P = 0.455). The dichotomization process differed widely across studies, with a progression definition ranging from a worsening of fibrosis unit between two biopsies to a fixed higher fibrosis score value at the second biopsy (Table 2).

DISCUSSION

Viral factors have usually been considered to have limited influence on liver FPR in chronically infected HCV patients [29]. However, recent studies highlighted a possible association between viral genotypes and rapid fibrosis progression. By pooling results from several, often small-sized studies, this meta-analysis provides a comprehensive summary of the published literature on the topic as well as new insights into the natural history of chronic HCV infection. The pooled analyses of eight single-biopsy studies clearly confirmed a significantly faster progression for genotype 3 patients compared with the other genotypes. Among them, five showed a significantly faster fibrosis progression or a clear trend towards faster progression for genotype 3-infected patients compared with others [5–7,16,22]. The failure of some studies to detect a significant effect for viral genotype 3 probably results from their insufficient sample size (i.e. 342 cases and 684 controls are necessary for 80% power to detect an OR of 1.5 for viral genotype 3 on fibrosis progression, considering a 30% prevalence of this genotype). Despite a much smaller observation time, the pooled analysis of eight paired biopsies studies showed a trend towards faster

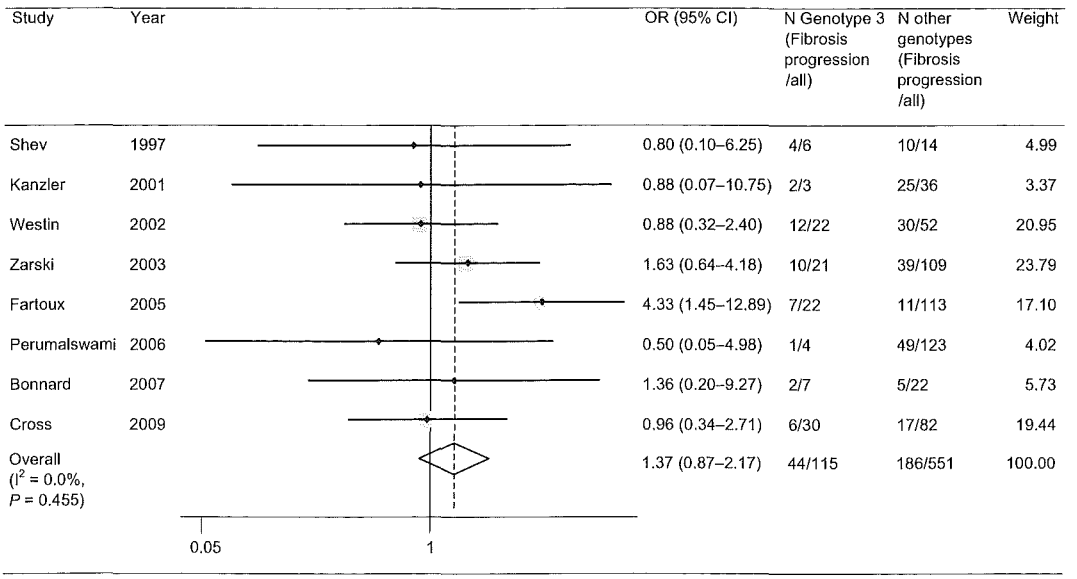

Fig. 4 Forest plot of odds ratio of fibrosis progression between two liver biopsies, genotype 3 *vs* non-3. OR, odds ratio; 95% CI, 95% confidence interval.

progression for genotype 3-infected compared with genotype non-3-infected patients.

A previous study assessing stage-specific FPR using a Markov model suggested that viral genotype 1 (compared with other genotypes) may influence fibrosis progression, but the estimation was performed using a meta-regression [30]. It is known that such ecological associations may lead to incorrect estimates of the relation for individual patients.

The association of viral genotype 3 with FPR may have important practical implications. It has been reported that the uptake of antiviral therapy for hepatitis C has been declining during recent years [31]. Apart from poor rate of diagnosis and lack of referral, two major factors may account for this trend: the widespread perception on the supposedly slow average progression rate of hepatitis C, coupled with the huge expectations surrounding novel, more effective direct antiviral agents (DAA), to be first marketed in 2011–2012. Genotype 3-infected patients should be aware of a potentially faster progression rate and may benefit from individualized counselling, with particular attention given to the controllable factors, such as alcohol consumption and overweight [32]. While therapy with peginterferon alpha and ribavirin usually achieves 70–80% of sustained viral response among patients infected with HCV genotype 3, certain subgroups of patients still have high relapse rates, such as those with elevated baseline viral load (>800 000 copies/mL, [33,34]) and advanced fibrosis [32]. Patients with chronic hepatitis C may be deferred from current treatment regimens just because more potent DAA will be licensed in the near future [35]. However, this 'warehousing' attitude may not be justified in infections with genotype 3, given that the serine protease inhibitors, such as telaprevir, have very limited activity against genotype 3 [36]. DAAs with significant activity against genotype 3, such as the nucleoside RNA polymerase inhibitor R7128 [37] or the cyclophilin-binding molecule Debio 025 [38], are far from completing clinical development. These considerations argue against the indiscriminate deferral from antiviral therapy in patients infected with genotype 3.

Multiple reasons may explain why paired biopsies studies did not show a significant effect of genotype 3. First, confounding by indication is likely to be a major problem in paired biopsies studies, as only selected patients undergo a second biopsy (e.g. those with multiple comorbidities and potentially rapidly evolving liver disease). Second, paired biopsies studies have a smaller sample size than single-biopsy studies. Out of eight studies, none included more than 30 genotype 3 patients, and four included <7 genotype 3 patients, resulting in low power to detect a given ES. Third, paired biopsies studies have a much smaller observation time than single-biopsy studies (~5 years between 2 biopsies compared with ~13 years from the infection date to the first biopsy, Fig. S3). This short duration may not be sufficient to detect genotype-specific differences in terms of FPRs. Fourth, paired biopsies studies have used arbitrary cut-offs for dichotomizing the outcome into progression *vs* nonprogression, for instance a worsening of the score by one or several units [13–15,17,18,20,23] or reaching a specific fibrosis stage at the second biopsy [19]. This method results in more information loss if one considers that the process of fibrosis is continuous. Finally, given that FPRs are not constant over time, paired biopsies studies may have included patients when the progression rate is the slowest (e.g. transition from Metavir scores F1–F2 [30] or F2–F3 [7]), making it even more difficult to detect genotype-specific differences (Fig. S2).

Table 2 Characteristics of participants in studies included in the meta-analysis

Reference	*N* participants, (*N* assessable)	Mean age at biopsy in years (±SD or 95% CI)	Mean age at infection (±SD or 95% CI)	Mean duration of HCV infection in years (±SD or 95%CI)	Mean FPR per year for genotypes 3 (±SD or 95% CI), *N* of patients	Mean FPR for genotypes non-3 (±SD or 95% CI), *N* of patients
Studies with FPR based on presumed date of infection and 1 liver biopsy						
Poynard *et al.* [11]	1157 (246)	46 (45–47)	–	12.4 (11.9–12.9)	0.17† (0.13–0.22), *N* = 39	0.12†, *N* = 207
Adinolfi *et al.* [16]	71 (40)	49† (range 20–66)	–	Genotype 1a:15† (range 6–24) Genotype 3a: 9† (range 3–18)	0.11 (±0.02), *N* = 25	0.07 (±0.01, genotype 1a only), *N* = 15
Martinez-Sierra *et al.* [12]	188 (188)	38 (34–39)	21† (19–23)	17.2 (16–19)	0.15 (0.10–0.20), *N* = 56	0.14 (0.11–0.016), *N* = 132
Hézode *et al.* [5]	267 (267)	43 (±10)	24 (±10)	10 (±7.8)	Proportion of rapid progressor‡ 49/66 (74%)	Proportion of rapid progressor‡ 84/201(41%)
Richardson *et al.* [21]	205 (205)	40 (±8)	22 (±8)	17.6 (±8.5)	Proportion of rapid progressor§ 26/88 (30%)	Proportion of rapid progressor§ 35/117 (30%)
Bochud *et al.*[7]	1189 (1189)	42† (IQR 13)	19† (IQR 9)	21† (IQR 13)	0.10, *N* = 327	0.07 (genotype 1 only), *N* = 862
Hissar *et al.* [6]	140 (140)	42 (±15)	29†	12.1 (±8.9)	0.28 (±0.27), *N* = 105	0.24 (±0.17), *N* = 35
Reiberger *et al.* [22]	74 (74)	37 (±10)	24 (±8)	13 (±5)	0.22 (±0.09), *N* = 24	0.19 (±0.08, genotype 1 only), *N* = 50

Table 2 (Continued)

Reference	Dichotomization process	*N* participants, (*N* assessable [7])	Mean age at infection (±SE or range)	Median age at first biopsy in years (range)	Median time between two biopsies in years (range)	Genotype 3: proportion with fibrosis progression (%)	Genotype non-3: proportion with fibrosis progression (%)
Studies with FPR estimated between 2 liver biopsies							
Shev *et al.* [13]	Knodell total score worsening by ≥2 units between biopsies	20 (19)	–	30 (16–56)	12 (9–16)	4/6 (67)	10/14 (71)
Kanzler *et al.* [23]	Knodell/Chevallier fibrosis score worsening by ≥1 unit	39 (39)	–	–	2.3 (1–5.1)	2/3 (66)	25/36 (69)
Westin *et al.* [18]	Ishak fibrosis score worsening by ≥1 unit	74 (74)	–	a. Progressor: 37[†] b. Non-progressor: 34[†]	a. 6.5[†] (IQR 3.9–10.6) b. 5.5[†] (IQR 2.5–7.7)	12/22 (55)	30/52 (57)
Zarski *et al.* [14]	METAVIR fibrosis score worsening by ≥1 unit	130 (130)	26 (±12)	–	3.6 (±2.6)	10/21 (48)	39/109 (36)
Fartoux *et al.* [19]	METAVIR fibrosis score of 3 or 4 at second biopsy	135 (135)	–	–	5.0 (1.5–13.16)	7/22 (32)	11/113 (10)
Perumalswami *et al.* [20]	Ishak fibrosis score worsening by ≥1 unit	136 (127)	29 (8–67)	a. Progressor: 44 (21–67) b. Non-progressor: 41 (19–67)	3.6 (0.5–17)	1/4 (25)	49/123 (40)
Bonnard *et al.* [15]	METAVIR fibrosis score worsening by ≥2 units	32 (29)	–	a. Rapid progressor: 45[†] (34–53) b. Slow progressor: 43[†] (35–64)	4.1[†] (2–6.7)	2/7 (29)	5/22 (23)
Cross *et al.* [17]	Ishak fibrosis score worsening by ≥1 unit	112 (106)	–	44[†] (IQR 39–51)	4.2[†] (IQR 2.8–6)	6/30 (20)	17/76 (22)

N, number; SD, standard deviation; SE, standard error; FPR, fibrosis progression rate; CI, confidence interval; IQR, Interquartile Range.
[†]Denotes median (95% CI, IQR or range) instead of mean. [‡]Rapid progressor = Fibrosis progression rate >0.074 U/year METAVIR. [§]Rapid progressor = Scheuer stage 3 or 4 on biopsy or fibrosis stage 2 on biopsy ≤10 years after HCV acquisition.

As in many systematic reviews, the limitation of this study results from the limitation of the original studies themselves. Those include the inability to precisely determine the date of infection, the variability in the assessment of fibrosis staging, the nonlinearity of fibrosis progression over time, the failure to account for multiple risk factors. However, several studies addressed these issues. In three studies, the role of viral genotype 3 in fibrosis progression was confirmed in multivariate analyses, accounting for different covariates such as age, alcohol consumption and steatosis [5–7]. In one of them, the authors suggested that cannabis use, which may be more prevalent among genotype 3-infected patient, may have been a confounding factor for the role of genotype 3. However, this study clearly identified cannabis use, genotype 3, age at infection, alcohol intake and steatosis all as independent risk factors for rapid fibrosis progression (>0.74 U/year) in a stepwise logistic regression model of 267 patients [5]. In another study, the association of genotype 3 with faster progression remained significant among patients infected by blood transfusion (for whom the date of infection is certain), among different age groups, or among different periods of infection, and when using different methods to assess the progression rate [7].

Owing to our stringent selection criteria, the number of studies included in the meta-analysis is relatively small. Therefore, it was not possible to perform a meta-regression analysis and explore the role of potential confounders. We could not include a large confirmatory study (N = 327, N genotype 3 = 80), showing that patients infected with HCV genotype 3 had shorter time to infection than others, because it did not provide FPR rates [39].

This study provides new insight into the natural history of HCV infection. The evidence for a role of genotype 3 in fibrosis progression may have important implications for the management of patients infected with this genotype.

ACKNOWLEDGEMENT

PYB is supported by the Swiss National Science Foundation (32003B_127613/1), the Leenaards Foundation and the Santos-Suarez Foundation. MB is supported by the Swiss School of Public Health Plus.

REFERENCES

1 Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol* 2006; 44(1 Suppl.): S6–S9.
2 Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001; 345(1): 41–52.
3 Massard J, Ratziu V, Thabut D *et al.* Natural history and predictors of disease severity in chronic hepatitis C. *J Hepatol* 2006; 44(1 Suppl.): S19–S24.
4 Missiha SB, Ostrowski M, Heathcote EJ. Disease progression in chronic hepatitis C: modifiable and nonmodifiable factors. *Gastroenterology* 2008; 134(6): 1699–1714.
5 Hezode C, Roudot-Thoraval F, Nguyen S *et al.* Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology* 2005; 42(1): 63–71.
6 Hissar SS, Kumar M, Tyagi P *et al.* Natural history of hepatic fibrosis progression in chronic hepatitis C virus infection in India. *J Gastroenterol Hepatol* 2009; 24(4): 581–587.
7 Bochud PY, Cai T, Overbeck K *et al.* Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. *J Hepatol* 2009; 51(4): 655–666.
8 Liberati A, Altman DG, Tetzlaff J *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; 6(7): e1000100.
9 Hedges LV. Distribution theory for glass's estimator of effect size and related estimators. *J Edu Stat* 1981; 6(2): 107–128.
10 Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. *Stat Med* 2000; 19(22): 3127–3131.
11 Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; 349(9055): 825–832.
12 Martinez-Sierra C, Arizcorreta A, Díaz F *et al.* Progression of chronic hepatitis C to liver fibrosis and cirrhosis in patients coinfected with hepatitis C virus and human immunodeficiency virus. *Clin Infect Dis* 2003; 36(4): 491–498.
13 Shev S, Dhillon AP, Lindh M *et al.* The importance of cofactors in the histologic progression of minimal and mild chronic hepatitis C. *Liver* 1997; 17(5): 215–223.
14 Zarski J, Mc Hutchison J, Bronowicki J *et al.* Rate of natural disease progression in patients with chronic hepatitis C. *J Hepatol* 2003; 38(3): 307–314.
15 Bonnard P, Lescure FX, Amiel C *et al.* Documented rapid course of hepatic fibrosis between two biopsies in patients coinfected by HIV and HCV despite high CD4 cell count. *J Viral Hepat* 2007; 14(11): 806–811.
16 Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001; 33(6): 1358–1364.
17 Cross TJ, Quaglia A, Hughes S, Joshi D, Harrison PM. The impact of hepatic steatosis on the natural history of chronic hepatitis C infection. *J Viral Hepat* 2009; 16(7): 492–499.
18 Westin J, Lagging L, Spak F *et al.* Moderate alcohol intake increases fibrosis progression in untreated patients with hepatitis C virus infection. *J Viral Hepat* 2002; 9(3): 235–241.
19 Fartoux L, Poujol-Robert A, Guéchot J, Wendum D, Poupon R, Serfaty L. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. *Gut* 2005; 54(7): 1003–1008.

20 Perumalswami P, Kleiner DE, Lutchman G *et al.* Steatosis and progression of fibrosis in untreated patients with chronic hepatitis C infection. *Hepatology* 2006; 43(4): 780–787.
21 Richardson MM, Powell EE, Barrie HD, Clouston AD, Purdie DM, Jonsson JR. A combination of genetic polymorphisms increases the risk of progressive disease in chronic hepatitis C. *J Med Genet* 2005; 42(7): e45.
22 Reiberger T, Ferlitsch A, Sieghart W *et al.* HIV-HCV co-infected patients with low CD4+ cell nadirs are at risk for faster fibrosis progression and portal hypertension. *J Viral Hepat* 2010; 17(6): 400–409.
23 Kanzler S, Baumann M, Schirmacher P *et al.* Prediction of progressive liver fibrosis in hepatitis C infection by serum and tissue levels of transforming growth factor-beta. *J Viral Hepat* 2001; 8(6): 430–437.
24 Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology* 1994; 20(1 Pt 1): 15–20.
25 Ishak K, Baptista A, Bianchi L *et al.* Histological grading and staging of chronic hepatitis. *J Hepatol* 1995; 22(6): 696–699.
26 Knodell RG, Ishak KG, Black WC *et al.* Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981; 1(5): 431–435.
27 Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; 19(6): 1513–1520.
28 Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol* 1991; 13(3): 372–374.
29 Castera L, Hezode C, Roudot-Thoraval F *et al.* Worsening of steatosis is an independent factor of fibrosis progression in untreated patients with chronic hepatitis C and paired liver biopsies. *Gut* 2003; 52(2): 288–292.
30 Thein H, Yi Q, Dore G, Krahn M. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008; 48(2): 418–431.
31 Volk ML, Tocco R, Saini S, Lok AS. Public health impact of antiviral therapy for hepatitis C in the United States. *Hepatology* 2009; 50(6): 1750–1755.
32 Zeuzem S. Forewarned is forearmed. *J Hepatol* 2009; 51(4): 626–627.
33 Shiffman ML, Suter F, Bacon BR *et al.* Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007; 357(2): 124–134.
34 Zeuzem S, Hultcrantz R, Bourliere M *et al.* Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol* 2004; 40(6): 993–999.
35 Hezode C, Forestier N, Dusheiko G *et al.* Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; 360(18): 1839–1850.
36 Foster GR, Hezode C, Bronowicki J-P *et al.* Activity of telaprevir alone or in combination with peginterferon alfa-2A and ribavirin in treatment-naive genotype 2 and 3 hepatitis C patients: final results of study C209. *J Hepatol* 2010; 52(Suppl. 1): S27.
37 Gane EJ, Rodriguez-Torres M, Nelson DR, Jacobson IM, McHutchison JG, Jeffers L, Beard A. Antiviral activity of the HCV nucleoside polymerase inhibitor R7128 in HCV genotype 2 and 3 prior non-responders: results of R7128 1500mg BID with PEG-IFN and ribavirin for 28 days. *Hepatology* 2008; 48(Suppl. 4): LB10.
38 Flisiak R, Horban A, Gallay P *et al.* The cyclophilin inhibitor Debio-025 shows potent anti-hepatitis C effect in patients coinfected with hepatitis C and human immunodeficiency virus. *Hepatology* 2008; 47(3): 817–826.
39 De Nicola S, Aghemo A, Rumi MG, Colombo M. HCV genotype 3: an independent predictor of fibrosis progression in chronic hepatitis C. *J Hepatol* 2009; 51(5): 964–966.
40 Chevallier M, Guerret S, Chossegros P, Gerard F, Grimaud JA. A histological semiquantitative scoring system for evaluation of hepatic fibrosis in needle liver biopsy specimens: comparison with morphometric studies. *Hepatology* 1994; 20(2): 349–355.

APPENDIX 1

Detailed statistic analysis

For single biopsy studies both dichotomous and continuous outcome were transformed into a comparable effect size (ES, i.e. the difference in mean fibrosis progression rate between genotype 3 and other genotypes divided by its standard deviation). Using an ES allows us to compare different fibrosis scores. Briefly, an effect size is a unitless measure of comparison for results reported in different scales. A larger fibrosis scale will have a larger difference in means and also a larger standard deviation, thus the effect size will be comparable whichever scale is used. For fibrosis progression, a positive ES indicates that people infected by genotype 3 had a faster fibrosis progression rate. For continuous FPR, the mean and the standard deviation (either provided or converted from the confidence intervals) for each viral genotype were extracted. For one study reporting the median instead of the mean, we assumed that median equaled mean. The means and the standard deviations of all genotypes non-3 were added using the additive properties of the variance. We derived ES and standard deviations from FPR using the unbiased estimate of Hedges' effect size (9). For each study giving FPR as a dichotomous outcome, the odds ratio (OR) for comparison of genotype 3 *vs* others was calculated. We converted OR to ES by using the method described by Chinn (10). The author shows that when assuming a logistic distribution with equal variances between the two groups, the natural logarithm of the OR equal a constant multiplied by the ES. The standard logistic distribution has variance $\pi^2/3$, so a difference in ln(OR)

can be converted to an approximate ES by dividing the ln(OR) by $\pi/\sqrt{3}$ which is 1.81. For both meta-analyses, we calculate the statistical heterogeneity using a I^2 calculation. This calculation provides an estimate of the variation of variance among studies due to true heterogeneity rather than chance. Publication bias was graphically evaluated using a funnel plot of the ES (or OR) for asymmetry resulting from the nonpublication of small negative studies.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Forest plot of fibrosis progression rates estimated from one biopsy, genotype 3 *vs* other genotypes stratified by multivariable analysis.

Figure S2. Fibrosis progression rates for Metavir scores transition in patients infected with genotype 3 *vs* other genotypes.

Figure S3. Mean or median observation time in studies evaluating FPR either between an estimated date of infection or between two biopsies.

Table S1: Detailed material and methods.

Table S2: Further characteristics of participants in studies included in meta-analysis.

Table S3: Liver fibrosis staging.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

Impact of a Nurse Vaccination Program on Hepatitis B Immunity in a Swiss HIV Clinic

Noémie Boillat Blanco, MD, Arnold Probst, MD,* Vreneli Waelti Da Costa,* Stefano Giulieri, MD,* Enos Bernasconi, MD,† Alexandra Calmy, MD, PhD,‡ Luigia Elzi, MD,§ Andri Rauch, MD,|| Rainer Weber, MD,¶ Barbara Bertisch, MD,# Matthias Cavassini, MD,* and Pierre-Yves Bochud, MD**

Abstract: We evaluated the impact of a nurse program for hepatitis B virus vaccination in a center from the Swiss HIV Cohort Study. Immunity (anti-HBs >10 IU/mL) increased from 32% to 76% in the intervention center (n = 238) where vaccine management was endorsed by nurses, but only from 33% to 39% in control centers (n = 2712, $P < 0.001$) where management remained in charge of physicians. Immunity against HBV in the HIV population is insufficient in Switzerland. Specific nurse vaccination program may efficiently improve health care.

Key Words: Hepatitis B, HIV, nurse intervention, vaccination, vaccination coverage

(*J Acquir Immune Defic Syndr* 2011;58:472–474)

INTRODUCTION

Hepatitis B virus (HBV) can cause acute infection ranging from asymptomatic to fulminant hepatitis (<1%) depending on various host and viral factors. Chronic infection leading to cirrhosis and hepatocellular carcinoma occurs in a minority of patients. The incidence of acute HBV infection is higher in HIV-positive patients than in the general population (12.2 versus 0.33 cases/1000 person-years). Similarly, the prevalence of chronic HBV infection is higher in HIV-positive patients than in the general population (4%–10% versus <1%).[1]

The most efficient way to prevent HBV infection is vaccination, which is recommended by the Centers for Disease Control and Prevention for every HIV-positive patient.[2] HBV vaccine is safe and efficient. However, its immunogenicity is lower in HIV-positive patients (18%–61%) compared with immunocompetent subjects (90%–95%).[3] Risk factors for nonresponse to vaccination include older age, alcohol abuse, high HIV RNA, low CD4 T-cell count, and absence of combination antiretroviral therapy.[3] The number of vaccinated HIV-positive patients is largely insufficient in most countries, with 14%–62% of patients receiving at least 3 doses of vaccine.[1,4]

Strategies to improve the rate of HBV vaccination among high-risk populations included mainly free vaccination programs delivered to sex workers, men having sex with men, intravenous drug users or homeless.[5–7] To our knowledge, no studies have evaluated the efficacy of HBV vaccination programs in clinical practice among HIV-positive patients, population with a better follow-up than the population included in the aforementioned studies.

In 2006, an external audit in the Lausanne HIV center of the Swiss HIV Cohort Study (SHCS) showed that the medical files failed to report HBV vaccination coverage and immunity. We investigated the effectiveness of a nurse intervention program for systematic chart review and HBV vaccine management in our center.

METHODS

Patients recorded in the SHCS on January 1, 2007, were eligible for the study. The SHCS is an ongoing, continuous enrollment prospective observational cohort of HIV-1–infected patients followed at 7 medical centers in Switzerland.[8] Patients have been enrolled since 1988 and signed written consent for data collection and blood sampling. Ethical approval for this research was obtained from the institutional review boards. All SHCS participants were included in the study, except participants with previous HBV infection (anti-HBc or HBs antigen positive). Patients who were immune (anti-HBs ≥ 10 IU/L), not immune (negative HBV serologic markers), or had an unknown immunity (no anti-HBs check) for HBV in January 2007 were followed up until June 2010. In

Received for publication June 7, 2011; accepted September 13, 2011.

From the *Department of Medicine, Infectious Diseases Service, University Hospital and University of Lausanne, Lausanne, Switzerland; †Division of Infectious Diseases, Hospital of Lugano, Lugano, Switzerland; ‡Division of Infectious Diseases, Geneva University Hospital, Geneva, Switzerland; §Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland; ||University Clinic of Infectious Diseases, University Hospital Bern and University of Bern, Bern, Switzerland; ¶Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland; and #Division of Infectious Diseases, Department of Medicine, Cantonal Hospital, St. Gallen, Switzerland.

This study was performed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation. Ethical approval for this research was obtained from the institutional review boards. P.Y.B. is supported by the Swiss National Science Foundation (32003B_127613 / 1), the Leenaards Foundation, and the Santos-Suarez Foundation.

The authors N.B.B., A.P., M.C., and P.Y.B. contributed equally to this work.

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Correspondence to: Pierre-Yves Bochud, MD, Department of Medicine, Infectious Diseases Service, University Hospital and University of Lausanne, BH 08-658, 1011 Lausanne, Switzerland (e-mail: pierre-yves.bochud@chuv.ch).

addition, nonimmune patients (anti-HBs <10 IU/L) and patients with unknown immunity were eligible for nurse vaccination program in the intervention center. Six other centers of the SHCS did not undergo any vaccine intervention and were used as control. In all these centers, HBV vaccination was prescribed by the physician in charge of the patient. The nurse intervention consisted of (1) documenting HBV serostatus in all patients with previously missing information, (2) providing vaccination (3 doses with a minimal interval of 1 and 6 months) to all nonimmune patients, (3) measuring vaccination effectiveness 1–12 months after the third dose, and (4) providing a second course of vaccination (according to the physician in charge) to nonresponders (anti-HBs < 10 IU/L). Clinical and demographic data were extracted from the SHCS database. Because vaccination history is not recorded in the SHCS database, it was obtained from medical records at the intervention center only.

HBV vaccine is available as a single-antigen formulation and in fixed combination. Two single-antigen formulations are available in Switzerland: Engerix-B (GlaxoSmithKline Biologicals, Rixensart, Belgium) and HBVAXPRO (Merck Research Laboratories, West Point, PA). One combination vaccine is available for adults: Twinrix (GlaxoSmithKline Biologicals, Rixensart, Belgium). Engerix and Twinrix formulations contain 20 μg and HBVAXPRO 10–40 μg/mL of HBsAg protein.

Group comparison was done using T test for continuous variable or χ^2 test for categorical variable. Statistical level for significance were assigned for P value lower than 0.05. Logistic regression was used for univariate and multivariate calculation of odds ratios. Variables with a significant P value on univariate analysis were used as covariate in the multivariate model. Statistical analyses were performed using Stata software (StataCorp, College Station, TX, version 11.1).

RESULTS

Among 6098 study patients, 3148 had a previous HBV infection (anti-HBc or HBs antigen positive). Among the 2950 uninfected patients, only 956 (32%) were immune against HBV, although 1782 (60%) were not immune and 212 (7%) had unknown immunity (Fig. 1). Lack of HBV immunity was associated with older age ($P < 0.001$) and low CD4 T-cell counts ($P = 0.006$; see **Table, Supplemental Digital Content 1**, http://links.lww.com/QAI/A225). Infection by homosexual contact or IV drug use demonstrated reduced odds for lack of immunity ($P < 0.001$ and $P = 0.01$, respectively) compared with infection by heterosexual contact. Furthermore, at baseline in January 2007, there was an important center effect (increased risk in centers 1, 3, 4, 5, 6 compared with center 0, all $P < 0.001$). In the intervention center, among the 124 nonimmune patients before the vaccination program, 58 (47%) were not vaccinated, 58 other (47%) were vaccine nonresponders after at least 3 vaccine doses, whereas the remaining 8 patients had an incomplete or undocumented vaccination.

During the study period, the number of immune patients increased from 76 (32%) to 180 (76%) in the intervention center, but only from 880 (33%) to 1057 (39%) in the control

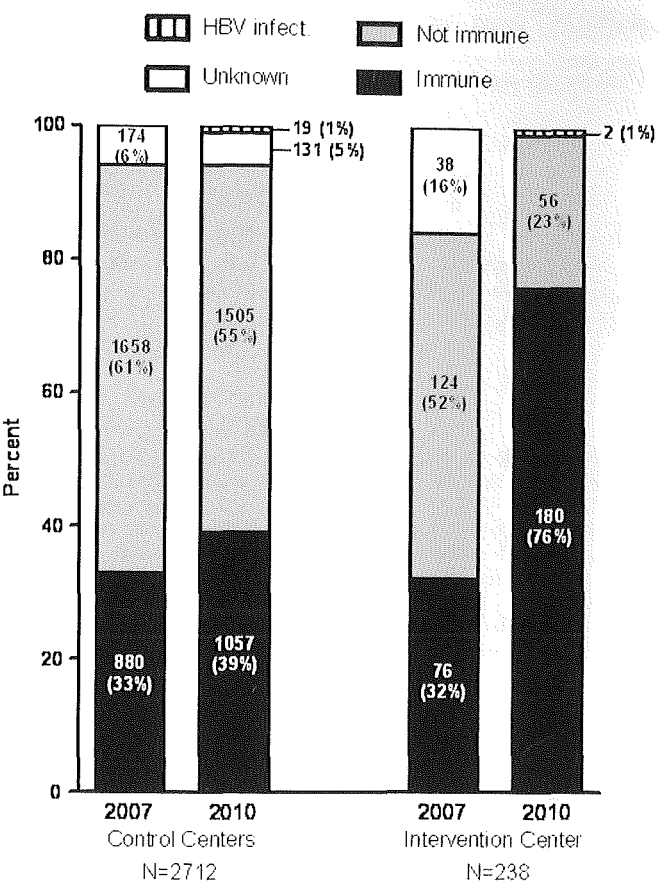

FIGURE 1. Evolution of the HBV immune status between 2007 and 2010 in the intervention and control centers.

centers (ie, 137% increase versus 20% increase, $P < 0.001$). The number of patients with undocumented serostatus decreased from 38 (16%) to 0 (0%) in the intervention center, but only from 174 (6%) to 131 (5%) in the control centers (ie, 100% versus 25% decrease, $P < 0.001$, Fig. 1).

Two patients (0.8%) in the intervention center and 19 (0.7%) in the control centers ($P = 0.9$) developed new HBV infections, all of which resolved spontaneously. In the intervention center, 1 of the 2 infections occurred at the beginning of 2007 (ie, before vaccination was proposed) and the other occurred in a vaccine nonresponder. We do not have details on the vaccination history of the 9 patients followed up in the control centers. After the vaccination program, 56 patients remained not immune in the intervention center. The reasons for persisting lack of immunity after the intervention were vaccine nonresponse (36 patients, 64%) and vaccine refusal (11 patients, 20%). Nine patients (16%) were in the course of vaccination at the time of analysis. No factor was significantly associated with nonresponse to vaccination in the intervention center, but the number of vaccine responders (n = 60) and nonresponders (n = 54) were small. However patients with HCV coinfection and absence of combination antiretroviral therapy had a worse vaccine response (both $P = 0.08$) (see **Table, Supplemental Digital Content 2**, http://links.lww.com/QAI/A226). The majority of patients (68%) received Engerix vaccine

formulation. The use of a specific type of vaccine did not influence vaccine response (see **Table, Supplemental Digital Content 2**, http://links.lww.com/QAI/A226).

DISCUSSION

Overall, this study shows that HBV immunity is insufficient in HIV-positive patients in Switzerland and can be significantly improved by a nurse vaccination program. It demonstrated that nonresponse to vaccination has only a minor impact on HBV immunity among HIV-positive patients.

Previously, intervention studies to improve the rate of HBV vaccination consisted mainly of free vaccine delivery to high-risk populations.[5–7] We identified only 3 studies in which the rate of vaccine coverage was reported before and after such an intervention. In a study conducted in different medicalized or nonmedicalized locations, such as sexually transmitted disease clinics, sites of methadone outlet, gay bars, homeless shelter, brothels or zones of street prostitution, free immunization compared with simple flyers distribution improved full vaccine coverage from 4% to 13%.[7] In another study performed in an urban sexually transmitted disease clinic, proposing an HBV fact sheet with free immunization compared with no specific intervention resulted in an improvement of full-vaccine coverage from 55% to 62%.[5] A nurse-managed program consisting of informative sessions plus targeted hepatitis education and tracking among homeless population versus standard targeted hepatitis education resulted in an improvement of full vaccine coverage from 54% to 68%.[6] Overall, previous interventions yielded only a modest improvement in HBV coverage compared with the marked improvement observed in our HIV clinic, where all patient charts were systematically reviewed.

Factors associated with lack of immunity in our study were older age and low CD4 T-cell count, which is concordant with previous studies (reviewed in 3). Infection through homosexual contact and intravenous drug use demonstrated reduced odds for lack of immunity, which is in opposition to other studies that observed lower seroconversion rates in homosexual compared to heterosexual patients.[9,10] The discordance with our results could be related the difference in vaccination rate rather than the availability to respond to vaccine. Indeed, these data suggest that homosexual and intravenous drug users have a higher vaccine coverage. We also found a strong center effect, which is concordant with another study.[11] The physicians are responsible for vaccination in every SHCS center, but the local habits and individual management may differ.

Overall, this study highlights the weak immunity against HBV among HIV-positive individuals in Switzerland and the significant impact of nurse intervention to improve the rate of immunization in this population.

ACKNOWLEDGMENTS

We thank the data managers (L. Musso, D. Alves) for providing the data and Y. Vallet and M. Rickenbach for informatics assistance and practical advice. We also thank the nurses (A. Mitouassiwou-Samba, R. Girard) for their participation in the vaccine intervention.

REFERENCES

1. Kellerman SE, Hanson DL, McNaghten AD, et al. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. *J Infect Dis*. 2003;188:571–577.
2. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep*. 2009;58 (RR-11):1–166.
3. Kim HN, Harrington RD, Crane HM, et al. Hepatitis B vaccination in HIV-infected adults: current evidence, recommendations and practical considerations. *Int J STD AIDS*. 2009;20:595–600.
4. Landrum ML, Huppler Hullsiek K, Ganesan A, et al. Hepatitis B vaccine responses in a large U.S. military cohort of HIV-infected individuals: another benefit of HAART in those with preserved CD4 count. *Vaccine*. 2009;27:4731–4738.
5. Gunn RA, Lee MA, Murray PJ, et al. Hepatitis B vaccination of men who have sex with men attending an urban STD clinic: impact of an ongoing vaccination program, 1998–2003. *Sex Transm Dis*. 2007;34:663–668.
6. Nyamathi A, Liu Y, Marfisee M, et al. Effects of a nurse-managed program on hepatitis A and B vaccine completion among homeless adults. *Nurs Res*. 2009;58:13–22.
7. Van Steenbergen JE. Results of an enhanced-outreach programme of hepatitis B vaccination in the Netherlands (1998–2000) among men who have sex with men, hard drug users, sex workers and heterosexual persons with multiple partners. *J Hepatol*. 2002;37:507–513.
8. Schoeni-Affolter F, Ledergerber B, Rickenbach M, et al. Cohort profile: the Swiss HIV Cohort study. *Int J Epidemiol*. 2010;39:1179–1189.
9. Fonseca MO, Pang LW, de Paula Cavalheiro N, et al. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine*. 2005;23: 2902–2908.
10. Wong EK, Bodsworth NJ, Slade MA, et al. Response to hepatitis B vaccination in a primary care setting: influence of HIV infection, CD4+ lymphocyte count and vaccination schedule. *Int J STD AIDS*. 1996;7: 490–494.
11. Myers C, Posfay-Barbe KM, Aebi C, et al. Determinants of vaccine immunity in the cohort of human immunodeficiency virus-infected children living in Switzerland. *Pediatr Infect Dis J*. 2009;28:996–1001.