

## Combined Pegylated Interferon and Ribavirin for the Management of Chronic Hepatitis C in a Prison Setting

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The elevated frequency of chronic hepatitis C virus (HCV) infection found among prison inmates, and the availability of improved pharmacological cure for this potentially life-threatening disorder, make investigations conducted in this somewhat neglected area very relevant, since only a few, open-label experiences have been reported till now. In the metropolitan prison of Bologna (Italy), HCV seroprevalence was found to be over 31% in 2003, so that a pilot feasibility study based on treatment with pegylated interferon plus ribavirin was initiated, after careful counseling carried out by a joint commission of health care personnel of the correctional facility and infectious diseases consultants. Thirty-nine patients were enrolled, and despite expected dropouts due to difficulty in maintaining the same level of counseling pressure over time, and the particularly unfavorable climatic conditions during Summer 2003, a sustained virological response was obtained for 8 out of the 21 patients who remained evaluable after the first three month follow-up, although we need to take into account that a high percentage of subjects (67%) were selected for therapy due to their favorable HCV genotypes (types 2 and 3). Our preliminary experience shows that an intrinsically complicated therapy, such as the administration of pegylated interferon plus ribavirin, can attain a relatively high success rate, even in a very unfavorable and uncomfortable context, such as a prison, where only enforced counseling, active participation of institutional health care operators, and patient's willingness to maintain an elevated level of co-operation and adherence, can overcome most structural and relational difficulties.

**Key Words:** Chronic hepatitis C, pegylated interferon, ribavirin, management, inmates, prison.

From an epidemiological point of view, prison inmates represent a relevant health problem, since the seroprevalence for hepatitis C virus (HCV) is very high in this population. Surveys conducted in the U.S.A. show a prevalence in inmates ranging from 16% up to 42% [1], while similar experiences carried out in Spain [2], England [3], and France [4], detected a frequency of 47.9%, 30%, and 30.3%, respectively. A recent Italian multicenter study disclosed a mean HCV prevalence of 38%, with broad variations found among the different institutions that participated in the very recent polycentric survey in Italy: 28% up to 50% [5]. In our recent epidemiological investigation involving 408 inmates at Bologna metropolitan prison, we found a seroprevalence rate for HCV of 31.1% [6].

While active action against the spread of HCV infection spread is important for the general population, HCV serological screening is of utmost importance, in order to have an early diagnosis of possibly severe and transmissible, but treatable, infectious diseases, as well as to trigger a educative and cultural process that leads prisoners to be more aware of the relevance of preventive measures, and therapeutic needs.

Received on 6 March 2006; revised 17 June 2006.

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**The Brazilian Journal of Infectious Diseases** 2006;10(4):274-278.  
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In such a process, expert counseling has a key role in the promotion of health care education in a difficult environment, such as a prison, where inmates are frequently refractive and poorly compliant with all proposals coming from prison institutions. Within this setting, pharmacological treatment with pegylated interferon and ribavirin for a serious and progressive disorder such as chronic hepatitis C, is an important opportunity to join medical care and improved awareness, so that it can be provided to all susceptible HCV-infected prisoners.

There is very little published information concerning treatment of chronic HCV infection in prisoners. In 2003, a four-year study on 90 patients with genotype 1 HCV disease reported a sustained virological response of 29% after treatment with interferon-alpha-2b associated with ribavirin [7]. Similar results were recently presented by Monarca et al. [5], but no controlled studies exist until now in this special population.

The management of HCV-infected prison inmates can give excellent results, but it is also burdened by several limitations. These include local logistical problems regarding the procedures for hepatic biopsy for histopathological examination; this procedure is not acceptable to most such patients, since they psychologically regard this act as an unacceptable physical threat. Furthermore, organizational aspects that depend on prison guardianship are not resolved with the necessary degree of flexibility to allow timely diagnostic examinations (i.e. the need to have an available military escort for examinations to be carried out in a hospital environment, without delay or bureaucracy limits). There are

also cultural and informational problems with inmates coming from abroad, who cannot speak Italian. Additionally, there are management problems in daily prison life and problems with interpersonal relations. Finally, low-level tolerability to any medical treatment (even though strong motivation has been stimulated and exhibited) is a well-known limitation for all diagnostic and therapeutic procedures recommended to prisoners, which can be exacerbated by underlying drug or alcohol abuse, as well as concurrent psychiatric disturbances. All these disadvantages may be circumvented or corrected when the proposed medical management is reinforced by strong personal motivation, stimulated by specific, empathic counseling, which should also continue after treatment has begun in order to explain expected side effects and encourage patients when they would otherwise suspend treatment due to such effects. Among possible advantages of medical treatment of inmates, this is a favorable environment for daily directly-observed therapy (DOT). This latter approach, [8] is expected to be the most effective method in a prison context, as has been clearly demonstrated.

### Material and Methods

A general cross-sectional serological screening for HCV antibodies, carried out at the Bologna prison in September, 2002, identified 127 HCV-positive patients. After careful counseling by the infectious disease consultant, together with the institutional medical and healthcare staff, with additional help by cultural mediators (when needed), and after written consent was obtained, 39 subjects were placed on combined interferon-ribavirin treatment. All study patients were followed and treated at the "Casa Circondariale di Bologna", during their detention period. Physical, hematological and biochemical exams were also performed at the prison facilities by a dedicated nurse team, while virological assays were performed at an external reference laboratory.

After beginning associated treatment, all patients were seen at the infectious disease ambulatory center of the prison on at least a monthly basis, depending on organizational constraints determined by prison rules and organization. During the summer of 2003 (July and August), as well as during Christmas and Easter vacations, the possibility to perform all visits as scheduled was significantly reduced, due to the reduced number of prison attendants and their increased daily duties. During the same period, periodical specialist and laboratory controls also decreased significantly, because of the simultaneous reduction in the number of available nurses during these critical periods.

Of 39 subjects who started the trial after their informed consent was obtained, 38 were males, and their mean age was 36.4 years; along with 35 Italian inmates, we also included four inmates who had immigrated from Northern Africa. At baseline, all patients were clinically stable, had a CD4+ lymphocyte count above 400 cells/ $\mu$ L and plasma HIV-RNA

levels ranging from undetectable (<50) to 10,000 copies/mL. All of them underwent concurrent HAART therapy containing at least three antiretroviral compounds, with estimated adherence levels above 90%. Five patients had prior or concurrent psychiatric co-morbidity, so that a psychiatric consultation became mandatory before treatment was initiated. Thirty-six of the 39 subjects were ex-i.v. opiate drug addicts, and 11 patients received oral methadone treatment at the time of initiation of interferon-ribavirin therapy.

All patients were treated with s.c. pegylated interferon-alpha 2b at 1.5 mcg/Kg/week, associated with oral ribavirin, using standard regimens, based on body weight, in order to assess both feasibility, efficacy, and safety of HCV treatment in this particular setting. The scheduled treatment duration was six and nine months for patients with HCV genotypes 3 and 2 and 1 and 4, respectively. Treatment interruption occurred earlier than recommended, due to seasonal limitations at our prison facilities (summer time, difficulty to perform drug administration and monitoring during this period, etc.).

Baseline criteria were selected in order to make access to treatment as easy as possible; it was also possible for patients without recent liver histopathology, especially when they had favorable genotypes (HCV genotypes 2 and 3). Thirteen of the 39 patients, who were predominantly affected by genotype 1 HCV hepatitis, had a liver biopsy during their previous medical screening. In 12 of them, active chronic HCV hepatitis was found, while in one patient progression to liver cirrhosis was detected. In our series, 19 of the 39 inmates had a genotype 1-HCV infection, while genotype 3 was detected in 20 of the 39. The overall, mean duration of known HCV disease was 8.5 years. Twelve patients had previous interferon treatment experiences; mostly of them had ended with early dropout due to intolerance or poor motivation.

In pre-treatment laboratory examinations, seven patients out of 39 were found to be HIV-HCV co-infected, so that HIV disease also needed tailored monitoring and treatment.

### Results

A flow-chart of study design, conduction, and outcome, is shown in Figure 1. Of 39 patients who started the scheduled therapeutic program, 18 dropped out during the first three months of treatment, while six more subjects interrupted their therapy between months four and six. A six-month follow-up performed six months after treatment interruption demonstrated persistence of HCV infection in 10 cases of 18, while three of the six patients who suspended therapy after four or more months had a sustained virological response, with HCV negativization attained (negative qualitative HCV-RNA bioassay), associated with normalization of serum AST-ALT values, all maintained even during subsequent control tests. Unfortunately, 11 inmates were lost to follow-up due to incidental causes, including release or transfer to other prisons.

Among the 21 patients who continued associated anti-HCV treatment beyond the fourth month, five showed persistently detectable HCV-RNA levels and were classified as non-responders (so that HCV therapy was interrupted based on updated recommendations). The remaining 16 subjects who continued their treatment were assessed at six months and showed a sustained, complete virological response in five cases, while two patients experienced a breakthrough of infection, and the remaining three subjects were lost to follow-up since their were moved from the Bologna prison.

When analyzing the phenomenon of early dropouts, in 8 out of 18 episodes this occurred happened during the summer of 2003, when there was particularly hot weather, with a mean seasonal temperature of 26.2°C, which was the most elevated since the 1967. The remaining early dropouts were concentrated during the Christmas and Easter holidays, when medical and nurse “coverage” is incomplete (due to the above-mentioned problems), and consequently infectious disease consultancies were also not possible within the planned intervals.

Among the most frequently experienced adverse effects of pegylated interferon-ribavirin therapy, we found a greater incidence of asthenia, fatigue, altered body temperature, arthromyalgia, anorexia, weight loss, headache, and paresthesia. In only two cases, a reduction of ribavirin dosage became necessary, because of emerging hematological abnormalities (drop of hemoglobin levels <10 g/L). No adverse clinical or laboratory effects attributable to the combination of anti-HCV and anti-HIV therapy were seen.

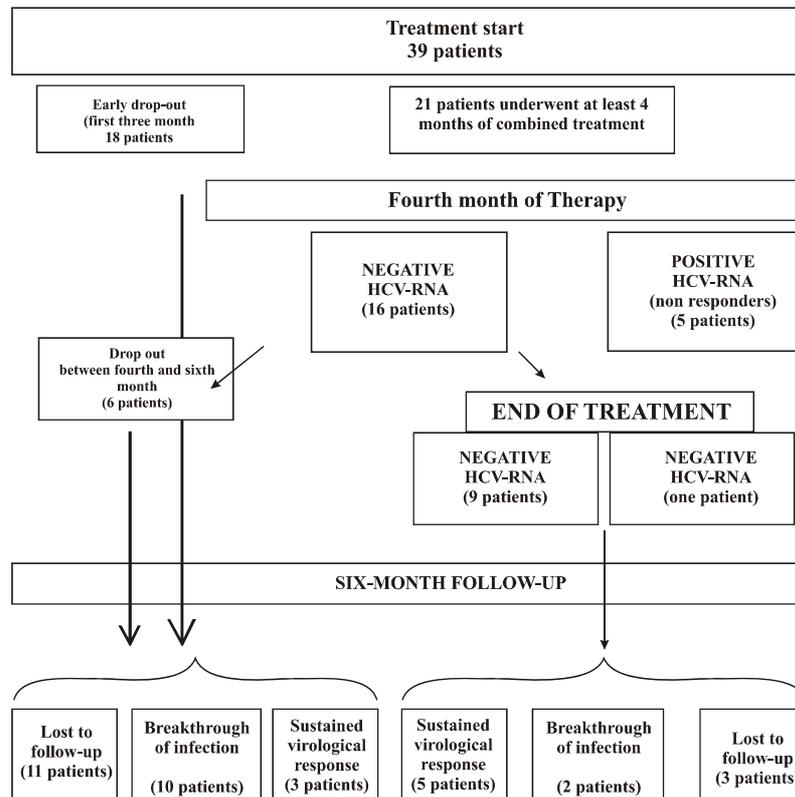
The overall early dropout rate was 46% of the initially enrolled patients, but it declined to 15% of overall subjects after the fourth month of treatment. Six months after the end of treatment, 20.5% of the inmates presented a sustained virological response characterized by steadily negative qualitative HCV-RNA testing. Most of this latter patient group with sustained therapeutic response, had HCV genotypes 3a and 2, and only one patient was infected by genotype 1 HCV.

The seven HIV-co-infected patients included six males and one female: four had HCV genotype 3a, and three had genotype 1. Five of these seven subjects were on antiretroviral therapy (HAART) before initiating combined interferon-ribavirin therapy. During the subsequent follow-up, four patients became early dropouts, one patient had no significant response, while a sustained virological outcome was obtained in the two remaining patients who completed the treatment course (both had HCV genotype 3, and were treated for six months).

**Discussion**

Field investigations on HCV management in patients experiencing “difficult” or “uncomfortable” personal and environmental conditions have been repeatedly recommended, based on all available, up-to-date guidelines [9], since data on these patient groups are still lacking. In particular, prisoners were pointed out as a specific high-risk population needing further investigation, as they include drug addicts, subjects

**Figure 1.** Study design and treatment course for our cohort of hepatitis C virus-infected inmates.



on methadone programs, and also individuals with prior, compensated psychiatric disorders (after comprehensive specialist assessments). We decided to answer some of these challenges, encouraged by the results of our initial, capillary counseling, which induced strong adherence and confidence to our proposals of an extensive serological screening for infectious hepatitis and HIV [6].

We hoped to maintain medical-nurse "pressure" and motivation for all patients who were found infected by HCV, hoping that uninterrupted contact and counseling would strongly encourage both initiation and follow-through of anti-HCV treatment, including in patients affected by the unavoidable side effects. Unfortunately, despite our efforts, external organizational deficits peaked during summer and holidays, so that our patients did not receive sufficient support from the prison personnel during intervals ranging from 15 to 55 days, which led to a significant reduction in specialist physical and laboratory controls and counseling by infectious disease specialists, and also decreased this very important support, especially when early untoward events became apparent, and needed active medical and nurse assistance. It seems unavoidable that these "external" biases acted unfavorably on patient motivation to continue therapy, and the expected high rate of dropouts, also exacerbated by concurrent judiciary decisions, and the lack of consistent medical support outside of the institution. Moreover, the unique hot weather experienced during the summer of 2003 may have significantly lowered tolerability levels, and worsened the effects of the expected interferon-ribavirin adverse events (including fever, sweating, anxiety, and the broad spectrum of flu-like symptoms, which become more difficult to control when there is very hot and wet weather and air-conditioning systems are not available).

When we consider our preliminary experience, which also shed light on possible, expected and unexpected negative issues, we now recommend that treatment not be initiated during summer (in temperate countries), deferring it to other seasons. Before scheduling such a binding therapeutic program, careful attention should be given to ensure no breaks in nursing-medical assistance and counseling for any reason, in order to overcome an excess of avoidable dropouts (above 10%-20% of cases). A network with other prisons, community health care facilities, and infectious disease reference centers, is also advisable, in order to permit continuity for inmates who abandon the institution, regardless of motives. Maximum flexibility for such an important health care program should be facilitated by all duty officers, since in the prison environment these operators play a key role in allowing each patient to follow a therapeutic program, including physical and laboratory examinations, drug administration, control of adverse events, and enforced counseling and motivation for initiating and/or continuing associated treatment for chronic HCV hepatitis. Regarding our choice to offer effective interferon-ribavirin therapy to inmates with a confirmed HCV

infection, elevated plasma HCV-RNA levels, and persistently abnormal serum transaminases; it was applied regardless of liver histopathology, especially when favorable HCV genotypes were present (i.e. genotypes 2 and 3). HIV-HCV co-infected patients did not show a significantly different course when compared with the remaining HCV-infected inmates, in terms of acceptance and efficacy of interferon-ribavirin treatment, even though five of seven patients also took antiretroviral therapy.

When we need to deal with "difficult" patients and in a "difficult" environment, such as a prison, such an approach allows a significantly-increased simplification and speeds up both diagnostic and therapeutic procedures, also improving patient adherence to health care recommendations. The choice of patients who should be placed on anti-HCV chemotherapy among inmates is quite problematic, due to intrinsically subjective and ever-changing aspects, especially when the actual predisposition to start and conduct antiviral treatment is investigated. The prison context exposes all inmates to the unpredictable possibility of transfers to other institutions, alternative detention measures, and release. It is evident that these conditions will significantly affect adherence, continuation, and subsequent success of anti-HCV therapy, even in patients who are highly motivated and encouraged by a preliminary, favorable response to treatment. However, a reduction of treatment to three months for non-1 genotypes appears to deserve further study [10].

Notwithstanding the limitations of our preliminary experience, we think that our intervention allowed us to obtain appreciable results from a strictly medical point of view, especially when taking into consideration the fact that published information on such populations is still very limited [7]. Moreover, the basis for a more targeted and effective intervention can now be proposed, making changes based on the pitfalls of this study. We think that such a complex treatment (necessary for chronic HCV hepatitis) is possible also for "difficult" patients, who have experienced drug addiction, alcohol consumption, immigration, and justice problems, despite an apparently unfavorable setting, such as in a prison, with its intrinsic difficulties.

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