HCV: LA PRATICA CLINICA
PAZIENTE TOSSICODIPENDENTE

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HCV, TOSSICODIPENDENZA, DAA

Fino a pochi anni fa i PWID erano esclusi dal trattamento

Aderenza

Eventi avversi

Reinfezione

Interazioni farmacologiche

Popolazione a > R di trasmissione

-- L'uso iniettivo di sostanze responsabile del 23% delle nuove infezioni

-- Ogni consumatore può infettare altri 20 consumatori nei primi 3 aa dal contagio

Oggi target prioritario

I PWID ottengono gli stessi risultati di SVR, con buoni livelli di aderenza e accettabilità

Research Article
Viral Hepatitis

JOURNAL OF HEPATOLOGY

Response to direct-acting antiviral therapy among ongoing drug users and people receiving opioid substitution therapy

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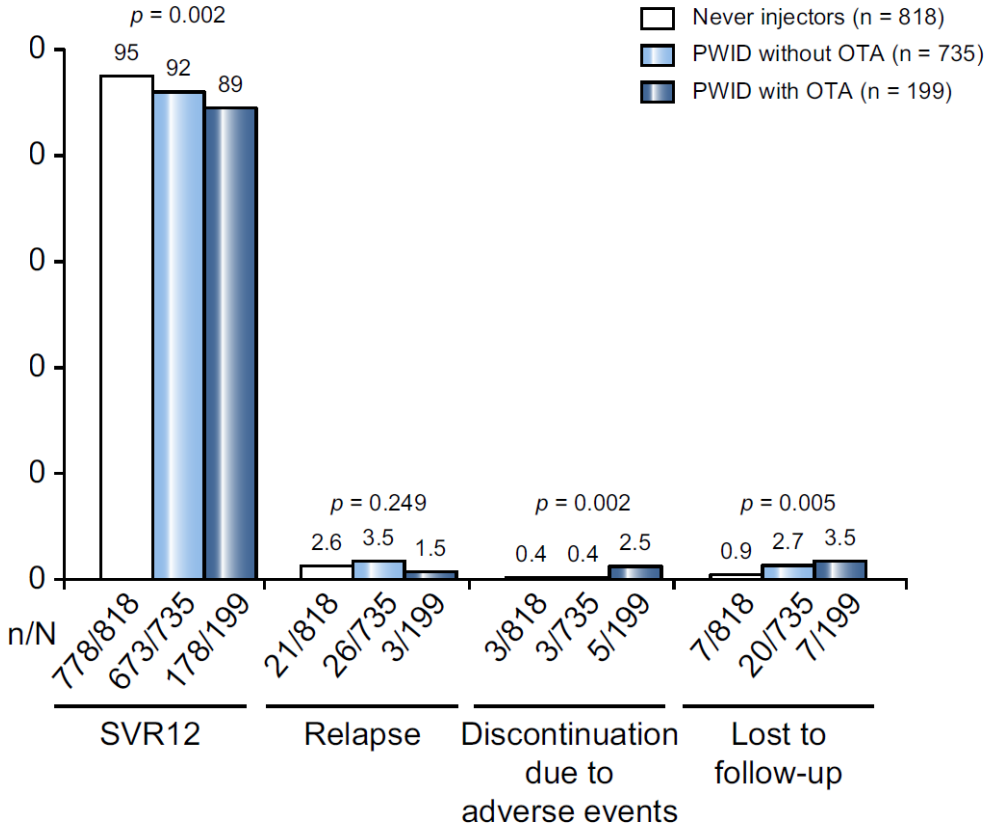

Background & Aims: People who inject drugs (PWID) and are on opioid agonist therapy (OAT) might have lower adherence to direct-acting antivirals (DAAs) against hepatitis C virus (HCV) and, therefore, lower rates of sustained virologic response (SVR). Because of this, we compared the SVR rates to interferon-free DAA combinations in individuals receiving OAT and those not receiving OAT in a real-world setting.

Methods: The HEPAVIR-DAA cohort, recruiting HIV/HCV-coinfected patients (NCT02057003), and the GEHEP-MONO cohort (NCT02333292), including HCV-monoinfected individuals, are ongoing prospective multicenter cohorts of patients receiving DAAs in clinical practice. We compared SVR 12 weeks after treatment (SVR12) in non-drug users and PWID, including those receiving or not receiving OAT. Intention-to-treat and per protocol analyses were performed.

Results: Overall, 1,752 patients started interferon-free DAA treatment. By intention-to-treat analysis, 778 (95%, 95% CI 93%–96%) never injectors, 673 (92%, 95% CI 89%–93%) PWID not on OAT and 177 (89%, 95% CI 83%–92%) PWID on OAT achieved SVR12 ($p = 0.002$). SVR12 rates for ongoing drug users (with or without OAT) were 68 (79%) compared with 1,548 (95%) for non-drug users ($p < 0.001$). Among ongoing drug users, 15 (17%) were lost-to-follow-up, and 3 (3.5%) became reinfected. In the per protocol analysis, 97% never injectors, 95% PWID not on OAT and 95% PWID on OAT achieved SVR12 ($p = 0.246$). After adjustment, ongoing drug use was associated with SVR12 (intention-to-treat) and OAT use was not.

Conclusions: HCV-infected PWID achieve high SVR12 rates with DAAs whether they are on OAT or not, but their response rates are lower than those of patients who never used drugs. This is mainly attributable to more frequent loss to follow-up. Accounting for active drug use during DAA therapy nearly closed the gap in SVR rates between the study groups.

Lay summary: Patients with hepatitis C virus infection who are on opioid agonist therapy can achieve high cure rates with current treatments. The use of illicit drugs during treatment can drive drop-outs and reduce cure rates. However, hepatitis C can be cured in most of those using drugs who complete treatment and follow-up.

CASO CLINICO

-- Uomo

-- 58 aa

-- Ex tossicodipendenza da oppiacei e cocaina ev in OST

-- Seguito regolarmente dal SERT, non uso di sostanze dal 2017

-- Fumatore

-- No potus

-- Epatopatia cronica da HCV nota dal 2001

-- OBI, HIV Neg, Lue Neg

2018

Genotipo 1a (dic 2017)

Eco addome (ott 2017): steatosi, non lesioni focali, milza nei limiti

Fibroscan (ott 2017): F2

AST/ALT nella norma

Naive a qualunque terapia anti HCV

Non uso di sostanze da 8 mesi

TP domiciliare: metadone 70 mg

12/02/2018

MAVYRET

8 settimane

13/03/2018
4 SETTIMANE

Buona compliance e aderenza
No effetti collaterali
HCVRNA 33 UI/ml
Transaminasi nella norma

10/04/2018
8 SETTIMANE

Buona compliance e aderenza
No effetti collaterali
HCVRNA <15 UI/ml
Transaminasi nella norma

31/07/2018
SVR12

HCVRNA <15 UI/ml

AST 15, ALT 14, Bil tot 0,7

GB 8880, PLT 180000, crea 0,98

NOVEMBRE 2018
…24 SETTIMANE DALLA FINE TERAPIA

HCVRNA
86600 UI/ml

AST 27, ALT 40, bil tot 0,5, gammaGT 24, crea 1,1, GB 8410, PLT 189000

LATE RELAPSE ?
REINFEZIONE ?

* Nega comportamenti a rischio
* Regolare followup al SERT con controlli settimanali tutti negativi
* Pz compliante

17/01/2019

HCVRNA 74300 UI/ml
Genotipo: 1 a
AST 27, ALT 32

Eco addome (dic 2018):
Lieve epatomegalia con ecostruttura omogenea a grana grossolana come per epatopatia diffusa, non lesioni focali

RESISTENZE

II. Sequence information

NS3 codons covered	1 - 181
NS3 region (w.r.t. H77)	S91A, L153V

III. Resistance analysis

Drug	Prediction		Scored Mutations
Asunaprevir	susceptible		none
Boceprevir	susceptible		none
Glecaprevir	susceptible		none
Grazoprevir	susceptible		none
Paritaprevir	susceptible		none
Simeprevir	susceptible		none
Telaprevir	susceptible		none
Voxilaprevir	susceptible		none

NS5A codons covered	1 - 213
NS5A region (w.r.t. H77)	S3P, F19S, F36S, V46A, H58D, F88S, Y93N, R123Q, S131T, I144V, A197T, L199V, A213T

III. Resistance analysis

Drug	Prediction		Scored Mutations
Daclatasvir	resistant		58D,93N
Elbasvir	resistant		58D,93N
Ledipasvir	resistant		58D,93N
Ombitasvir	resistant		58D,93N
Pibrentasvir	resistant		58D,93N
Velpatasvir	resistant		93N

II. Sequence information

NS5B codons covered	34 - 592
NS5B region (w.r.t. H77)	C46S, K50R, S62N, S90D, V116I, A117K, H118P, K124E, M173I, L184Q, Q206K, K209N, Q309R, T389I, L392F, N411NS, I424V, V432I, D437E, N444D, R510K, K523R, R531K, G543S, R544Q, T552K, S556G, H566R, L588Y

III. Resistance analysis

Drug	Prediction		Scored Mutations
Dasabuvir	resistant		444D,556G
Sofosbuvir	susceptible		none

geno2pheno®

HCV resistance prediction from genotype (version 1.0)

13/05/2019
RETREATMENT

Inizia VOSEVI
(Sofosbuvir/Velpatasvir/Voxilaprevir)
12 settimane

14/08/2019
FINE TERAPIA

HCVRNA<15 UI/ml
Transaminasi nella norma
Compliance e aderenza ottimali
No effetti collaterali

NOVEMBRE 2019
A 12 SETTIMANE DALLA FINE TP

SRV

HCVRNA <15 UI/ml

AST 22, ALT 17, gammaGT 14, bil tot 0,5, crea 0,96

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PREVISTO CONTROLLO A 24 SETTIMANE A FEBBRAIO 2019

Clinical Infectious Diseases

MAJOR ARTICLE

Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis

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Background. Treatment for hepatitis C virus (HCV) can lead to sustained virological response (SVR) in over 90% of people. Subsequent recurrence of HCV, either from late relapse or reinfection, reverses the beneficial effects of SVR.

Methods. A search identified studies analysing HCV recurrence post-SVR. The recurrence rate for each study was calculated using events/person years of follow-up (PYFU). Results were pooled using a random-effects model and used to calculate 5-year recurrence risk. Three patient groups were analysed: (1) Mono-HCV infected "low-risk" patients; (2) Mono-HCV infected "high-risk" patients (injecting drug users or prisoners); (3) human immunodeficiency virus (HIV)/HCV coinfected patients. Recurrence was defined as confirmed HCV RNA detectability post-SVR.

Results. In the 43 studies of HCV mono-infected "low-risk" patients (n = 7969) the pooled recurrence rate was 1.85/1000 PYFU (95% confidence interval [CI], .71–3.35; I^2 = 73%) leading to a summary 5-year recurrence risk of 0.95% (95% CI, .35%–1.69%). For the 14 studies of HCV monoinfected "high-risk" patients (n = 771) the pooled recurrence rate was 22.32/1000 PYFU (95% CI, 13.07–33.46; I^2 = 27%) leading to a summary 5-year risk of 10.67% (95% CI, 6.38%–15.66%). For the 4 studies of HIV/HCV coinfected patients the pooled recurrence rate was 32.02/1000 PYFU (95% CI, .00–123.49; I^2 = 96%) leading to a summary 5-year risk of 15.02% (95% CI, .00%–48.26%). The higher pooled estimates of recurrence in the high-risk and coinfected cohorts were driven by an increase in reinfection rather than late relapse.

Conclusions. SVR appears durable in the majority of patients at 5 years post-treatment. The large difference in 5 year event rate by risk group is driven mainly by an increased reinfection risk.

1. Stimare il tasso di ricorrenza in base al gruppo di rischio
2. Valutare il peso determinato da recidiva tardiva o reinfezione

Nel gruppo ad alto rischio (drug users, carcerati…), le ricorrenze erano dovute principalmente da reinfezioni (19.06/1000 PYFU)

HEPATITIS C LATE RELAPSE IN PATIENTS WITH DIRECTLY ACTING ANTIVIRAL- RELATED SUSTAINED VIROLOGICAL RESPONSE AT WEEK 12

Mariantonietta Pisaturo[1*], Carmine Minichini[1*], Mario Starace[1], Mara Caroprese[2], Margherita Macera[2], Giuseppina Brancaccio[2], Stefania De Pascalis[2], Antonella Santonicola[4], Alfonso Galeota Lanza[6], Rosa Zampino[7], Gaetano Cotticelli[5], Evangelista Sagnelli[1], Giovanni Battista Gaeta[2], Nicola Coppola[1,3].

Aim: The aim of the present study was to identify, among the patients with failure to DAA regimen, those with a late relapse (after the achievement of a sustained virological response at week 12) and to characterize the clinical, epidemiological and virological features of these patients.

Material and methods. 129 HCV patients with non-response to an IFN-free regimen were enrolled. Sanger sequencing of NS3, NS5A and NS5B was performed at failure by home-made protocols

Results. Of the 129 patients enrolled, 8 (6.2%) experienced a breakthrough, 15 (11.7%) non-response, 99 (76.7%) a relapse by week 12 after the end of DAA therapy, and 7 (5.4%) a late relapse (after week 12; median 24 weeks, range 24-72).

For 2 of the 7 patients with a late relapse a serum sample collected before the start of the DAA regimen was available; phylogenetic analysis showed no change in sequences of NS3, NS5A and NS5B regions, suggesting a reactivation of the initial HCV strain; for the remaining 5 patients, no serum collected before the DAA regimen was available and thus a re-infection cannot be excluded.

Conclusions. Although a late relapse is infrequent, the study suggests a post-treatment follow-up of 72 weeks.

lacking. The present real-life study showed that a DAA failure was observed in about 4% of 3,259 patients treated with DAA regimen; we underlined that 35% of failed patients were treated with a non-active or sub-optimal DAA regimen against HCV genotype. Moreover, our study

The identification of a re-infection has important implications for the choice of optimal retreatment strategies, since it is potentially simpler to treat due to the lack of exposure of the current viral quasispecies to therapy, whereas virological relapse cases may have selected viral variants with reduced susceptibility. Re-infection is a particular concern in patients with ongoing

Liver Int. 2019 May;39(5):844-853

LATE RELAPSE:
POSSIBILI CAUSE DI AUMENTATO RISCHIO DI RIATTIVAZIONE

- Persistenza di bassi livelli di virus a livello epatico
- Piccole quote di HCV RNA sierico <15UI/ml presenti a livello sierico
- Persistenza di HCV a livello extraepatico (PBMCs)

Liver Int. 2019 May;39(5):844-853

RIFLESSIONI

-- Le vere late relapse sono molto più rare delle re-infezioni
-- Pensare a nuovi modelli di cura: trattamento multidisciplinare e integrato (SER.D, infettivologo, infermieri, psicologo…)
-- Follow-up più prolungato nei soggetti a maggior rischio
-- Analisi filogenetica
-- Resistenze al baseline ?