SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

UNIFE

IL TRATTAMENTO DEL PAZIENTE ADULTO CON EPATITE CRONICA B: *LINEE GUIDA*

Silvia Carradori

Unita' Operativa Malattie Infettive Ospedaliera

Azienda Ospedale-Università S.Anna

-Societa' Medico Chirurgica

-02 Marzo 2013-

Guidelines and recommendations

- APASL (2005)
- Keeffe's Algorythms (2006)
- AASLD (2007)
- NIH (2007)
- Keeffe's Algorythms (2007)
- German guidelines (2007)
- Turkish TASL (2007)
- Belgian guidelines (2007)
- Pawlotsky (2008)
- APASL (2008)
- Dutch guidelines (2008)
- Polish guidelines (2008)
- Turkish VHSD (2008)
- EASL Clinical Practise Guidelines (2009)
- Recommendations from Italian workshop (2010)

•EASL 2012

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Issue 8 (April 2012) Revised Clinical Practice Guidelines on the Management of Chronic Hepatitis B

April 2012, in the run-up to The International Liver Congress™ 2012, EASL releases revised CPGs on the Management of Chronic Hepatitis B originally released in October 2008... read more

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ELSEVIER

Review article

Treatment of chronic hepatitis B: Update of the recommendations from the 2007 Italian Workshop☆

Giampiero Carosi[a,*,1], Mario Rizzetto[b,1], Alfredo Alberti[c,2], Giuseppe Cariti[d,2], Massimo Colombo[e,2], Antonio Craxì[f,2], Gaetano Filice[g,2], Massimo Levrero[h,2], Francesco Mazzotta[i,2], Giuseppe Pastore[j,2], Felice Piccinino[k,2], Daniele Prati[l,2], Giovanni Raimondo[m,2], Evangelista Sagnelli[k,2], Mario Toti[n,2], Maurizia Brunetto[o,3], Raffaele Bruno[g,3], Vito Di Marco[f,3], Carlo Ferrari[p,3], Giovanni B. Gaeta[k,3], Pietro Lampertico[e,3], Alfredo Marzano[b,3], Teresa Pollicino[l,3], Massimo Puoti[a,3], Teresa Santantonio[j,3], Antonina Smedile[a,3]

Regione Emilia-Romagna

Linee guida terapeutiche /3

Trattamento della epatite cronica B nell'adulto

con particolare riferimento agli analoghi nucleosidici/nucleotidici (NUC)

A cura del Gruppo multidisciplinare sui Farmaci per l'epatite cronica B Regione Emilia-Romagna

Direzione Generale alla Sanità e alle Politiche Sociali

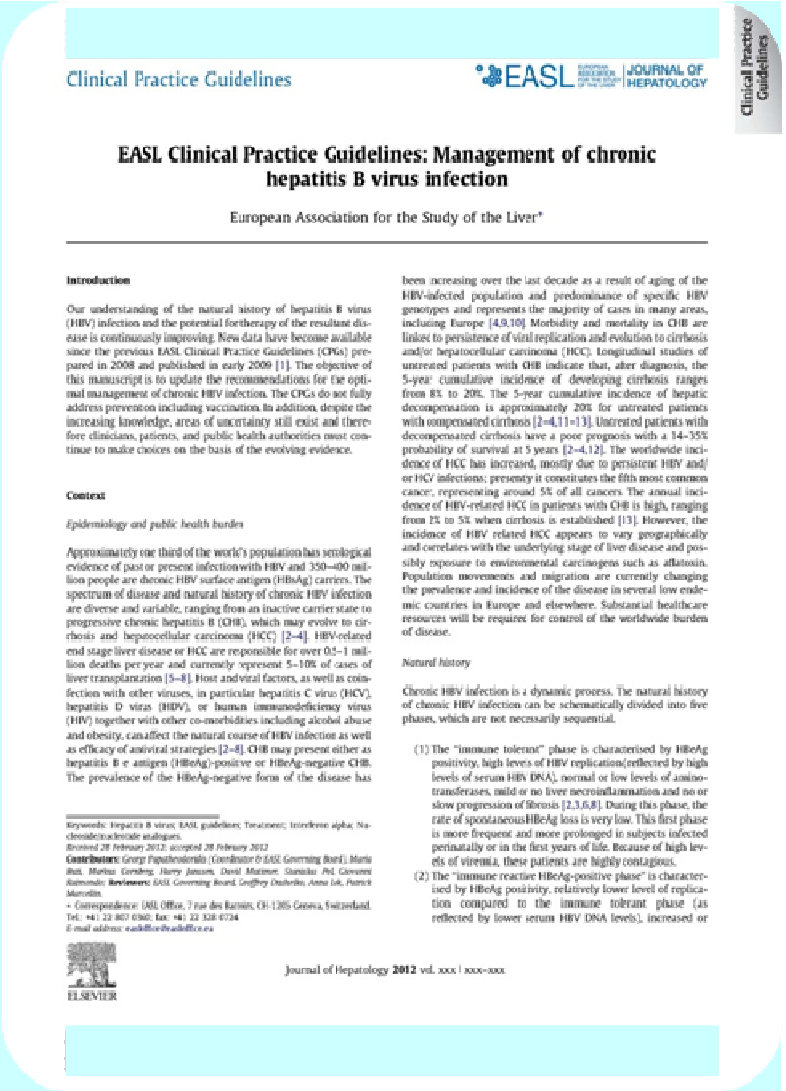
Linee guida terapeutiche n.3
Maggio 2010

EASL 2012 Clinical Practice Guidelines:

What is long-term treatment success in CHB and how do we achieve it?

"…to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) and death"

"This goal can be achieved if HBV replication can be suppressed in a sustained manner. Then, the accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and decreases the risk of HCC, particularly in non-cirrhotic patients"



Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

Introduction

Our understanding of the natural history of hepatitis B virus (HBV) infection and the potential for therapy of the resultant disease is continuously improving. New data have become available since the previous EASL Clinical Practice Guidelines (CPGs) prepared in 2008 and published in early 2009 [1]. The objective of this manuscript is to update the recommendations for the optimal management of chronic HBV infection. The CPGs do not fully address prevention including vaccination. In addition, despite the increasing knowledge, areas of uncertainty still exist and therefore clinicians, patients, and public health authorities must continue to make choices on the basis of the evolving evidence.

Context

Epidemiology and public health burden

Approximately one third of the world's population has serological evidence of past or present infection with HBV and 350–400 million people are chronic HBV surface antigen (HBsAg) carriers. The spectrum of disease and natural history of chronic HBV infection are diverse and variable, ranging from an inactive carrier state to progressive chronic hepatitis B (CHB), which may evolve to cirrhosis and hepatocellular carcinoma (HCC) [2–4]. HBV-related end stage liver disease or HCC are responsible for over 0.5–1 million deaths per year and currently represent 5–10% of cases of liver transplantation [5–8]. Host and viral factors, as well as coinfection with other viruses, in particular hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV) together with other co-morbidities including alcohol abuse and obesity, can affect the natural course of HBV infection as well as efficacy of antiviral strategies [2–8]. CHB may present either as hepatitis B e antigen (HBeAg)-positive or HBeAg-negative CHB. The prevalence of the HBeAg-negative form of the disease has been increasing over the last decade as a result of aging of the HBV-infected population and predominance of specific HBV genotypes and represents the majority of cases in many areas, including Europe [4,9,10]. Morbidity and mortality in CHB are linked to persistence of viral replication and evolution to cirrhosis and/or hepatocellular carcinoma (HCC). Longitudinal studies of untreated patients with CHB indicate that, after diagnosis, the 5-year cumulative incidence of developing cirrhosis ranges from 8% to 20%. The 5-year cumulative incidence of hepatic decompensation is approximately 20% for untreated patients with compensated cirrhosis [2–4,11–13]. Untreated patients with decompensated cirrhosis have a poor prognosis with a 14–35% probability of survival at 5 years [2–4,12]. The worldwide incidence of HCC has increased, mostly due to persistent HBV and/or HCV infections; presently it constitutes the fifth most common cancer, representing around 5% of all cancers. The annual incidence of HBV-related HCC in patients with CHB is high, ranging from 2% to 5% when cirrhosis is established [13]. However, the incidence of HBV related HCC appears to vary geographically and correlates with the underlying stage of liver disease and possibly exposure to environmental carcinogens such as aflatoxin. Population movements and migration are currently changing the prevalence and incidence of the disease in several low endemic countries in Europe and elsewhere. Substantial healthcare resources will be required for control of the worldwide burden of disease.

Natural history

Chronic HBV infection is a dynamic process. The natural history of chronic HBV infection can be schematically divided into five phases, which are not necessarily sequential.

(1) The "immune tolerant" phase is characterised by HBeAg positivity, high levels of HBV replication (reflected by high levels of serum HBV DNA), normal or low levels of aminotransferases, mild or no liver necroinflammation and no or slow progression of fibrosis [2,3,6,8]. During this phase, the rate of spontaneous HBeAg loss is very low. This first phase is more frequent and more prolonged in subjects infected perinatally or in the first years of life. Because of high levels of viremia, these patients are highly contagious.

(2) The "immune reactive HBeAg-positive phase" is characterised by HBeAg positivity, relatively lower level of replication compared to the immune tolerant phase (as reflected by lower serum HBV DNA levels), increased or

Keywords: Hepatitis B virus; EASL guidelines; Treatment; Interferon alpha; Nucleos(t)ide analogues.

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Contributors: George Papatheodoridis (Coordinator & EASL Governing Board), Maria Buti, Marina Cornberg, Harry Janssen, David Mutimer, Stanislas Pol, Giovanni Raimondo; Reviewers: EASL Governing Board, Geoffrey Dusheiko, Anna Isa, Patrick Marcellin.

* Correspondence: EASL Office, 7 rue des Battoirs, CH-1205 Geneva, Switzerland. Tel.: +41 22 807 0360; fax: +41 22 328 0724

E-mail address: easloffice@easloffice.eu

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Clinical Practice Guidelines

European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis Bvirus infection. *J Hepatol.* (2012), http://dx.doi.org/10.1016/j.jhep.2012.02.010.

QUESITI

1 CHI (QUANDO) TRATTARE ?

2 COME TRATTARE ?

3 COME MONITORARE I PZ. DURANTE IL TRATTAMENTO?

I PAZIENTI DA TRATTARE RIENTRANO IN 7 GRUPPI CHE HANNO INDICAZIONI, OBIETTIVI E STRATEGIE DIVERSE :

1. Pazienti con coinfezioni virali (HIV, HCV, HDV)
2. Pazienti sottoposti a terapie immunosoppressive
3. Pazienti in gravidanza
4. Pazienti pediatrici
5. Infezione acuta fulminante
6. Pazienti in dialisi e sottoposti a trapianto renale
7. Manifestazioni extraepatiche

EASL Clinical Practice Guidelines : Management of Chronic hepatitis B

Quali pz. trattare

Epatite cronica B

HBeAg positivo

Conosciuto anche come “wild type”

Anticorpi anti HBe negativi

HBV DNA > 20,000 IU/mL (>10^5 copie/ml)

HBeAg negativo (80-90% nelle nostre aree geografiche)

Conosciuto anche come “ variante HBeAg minus “ (pre-core , core promoter)

Anticorpi HBe positivi

HBV DNA > 2000 IU/mL (> 10^4 copie/mL)

Keeffe EB, et al. Clin Gastroenterol Hepatol. 2004;2:87-106.
Chu CJ, et al. Gastroenterology. 2003;125:444-451.

Current therapy: Antiviral drugs against HBV

IFN convenzionale e PEG-IFN

Lamivudina

Adefovir

Entecavir

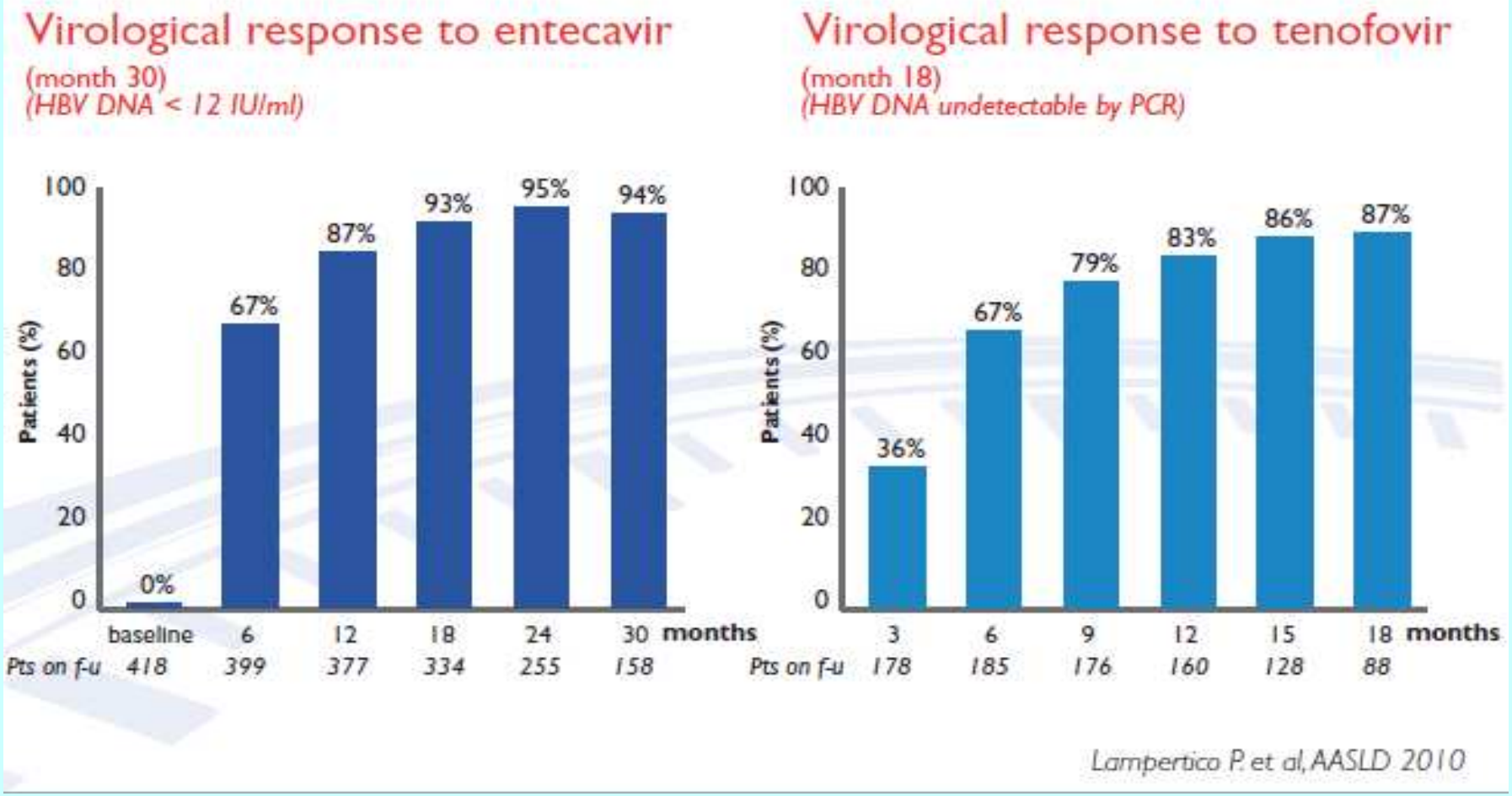
Telbivudina

Tenofovir

Analoghi Nucleot(s)idici

Composto	Nome commerciale	Dosaggio	Caratteristiche
Lamivudina (LVD)	Zeffix®	1 cp da 100 mg al dì	Alto tasso di resistenze (20% / anno) Non piu' indicata come monoterapia in prima linea
Adefovir (ADV)	Hepsera®	1 cp da 10 mg al dì	Tasso intermedio di resistenze (30% a 5 anni) Azione lenta, bassa potenza
Telbivudina (LTd)	Sebivo®	1 cp da 600 mg al dì	Tasso intermedio di resistenze (22% a 2 anni) Azione rapida e potente
Entecavir (ETV)	Baraclude®	1 cp da 0,5/1 mg al dì	Alta barriera genetica (resistenza 1.2% a 6 anni) ; Azione rapida e potente
Tenofovir((TDF)	Viread®	1 cp da 245 mg al dì	Alta barriera genetica (resistenza 0% a 5 anni); Azione rapida e potente
Peginterferon α 2a	Pegasys®	Iniezione da 180 mcg settimanale per 48 settimane	Azione antivirale e modulazione della risposta immune Effetti collaterali e controindicazioni

Real-world study : Italy cohort



Il tasso di soppressione dell' HBV DNA cresce e si mantiene nel tempo

Adapted from Lampertico P, et al. EASL 2012. Poster 522. Available at: Marcellin P. et al.; AASLD 2011 http://www.natap.org/2012/EASL/EASL_86.htm. Accessed May 2012.
Marcellin P. et al.; AASLD 2011

Raccomandazioni per la scelta degli NA

TRATTAMENTO DEI PAZIENTI NAIVE CON NUCs

Linee Guida	EASL	AASLD	Italian Workshop
Tenofovir	**1° scelta**	**1° scelta**	**1° scelta**
Entecavir	**1° scelta**	**1° scelta**	**1° scelta**
Adefovir	2° scelta	2° scelta	2° scelta
Lamivudina	2° scelta	2° scelta	2° scelta
Telbivudina	2° scelta	2° scelta	1° scelta

EASL guidelines, AASLD guidelines, Italian Workshop

Treatment strategies: how to treat

Long-term treatment with NAs

The most potent drugs with the optimal resistance profile, i.e. tenofovir or entecavir, should be used as first-line monotherapies **(A1)**

EASL – Clinical Practice Guidelines 2012

Pazienti Naïve con epatite cronica HBeAg positiva

	Epatite				Cirrosi	Cirrosi scompensata
Fibrosi	No	Lieve	Moderata	Severa		
METAVIR **Ishak's**	F0 S0	F1 S 1-2	**F2** **S3**	F3 S4	F4 S5-6	

Trattamento INDEFINITO con NAs

PEG IFN o
Trattamento FINITO con NAs

HBVDNA : > 20.000 UI/mL → **> 15 UI/mL**

ALT: > UNL → **ANY ALT**

Considerare trattamento

Trattare

OBBLIGATORIO

POSSIBILE **OPZIONALE**

Treatment of chronic hepatitis B: Update of the recommendations from the 2007 Italian Workshop, Digestive and Liver Disease Volume 43, Issue 4 2011

Pazienti Naïve con epatite cronica HBeAg negative

	Epatite				Cirrosi	Cirrosi scompensata
FIBROSI	No	Lieve	Moderata	Severa		
METAVIR **Ishak's**	F0 S0	F1 S 1-2	**F2** **S3**	F3 S4	F4 S5-6	

PEG IFN

Trattamento indefinito con NAs

Attività necroinf. > A2 (METAVIR) → **qualsiasi**

HBVDNA : > 2000 UI/mL → **> 15 UI/mL**

ALT: > UNL → **qualsiasi**

Considerare il trattamento

POSSIBILE **OPZIONALE**

Trattare

OBBLIGATORIO

Treatment of chronic hepatitis B: Update of the recommendations from the 2007 Italian Workshop, Digestive and Liver Disease Volume 43, Issue 4 2011

HBs Ag quantitativo

NEL PORTATORE INATTIVO

- **HBsAg quantitativo < 1000 UI / ml**
- **HBV DNA < 2000 UI / ml**

ACCURATEZZA DIAGNOSTICA 94,3%

VALORE PREDITTIVO POSITIVO 87, 9%

Brunetto MR, Gastroenterology 2010

Trattamento del paziente affetto da epatite cronica B

Trattamento di durata definita " curativo"

per avere un controllo immunologico sul virus che esiti in un mantenimento della risposta a fine ciclo di durata definita. (**HBV DNA < 2000 U; vn ALT**) **(A1)**

con Peg-IFNα (48 sett.) o NUCs (ETV o TDF) in pazienti HBeAg positivi

con Peg-IFNα (48 sett.) in pazienti anti-HBe positivi

Trattamento di durata indefinita "soppressivo"

per raggiungere e mantenere l'inibizione della replicazione virale e dell'attività di malattia con un trattamento antivirale prolungato nel tempo

con NUCs (ETV o TDF) in pazienti anti-HBe positivi

in pazienti HBeAg positivi che non sieroconvertono

[ETV: entecavir; TDF: tenofovir]

Carosi & Rizzetto, Dig Liver Dis 2008; 40:603-617
EASL- Clinical Practice Guidelines, J Hepatol 2012

When to stop NUC therapy ?

CHB Treatment Guidelines	EASL 2012 guidelines
HBeAg positive	A) confirmed anti-HBe seroconversion (and undectable HBV DNA) after at least 12 months of consolidation* B) confirmed HBsAg loss and anti-HBs seroconversion
HBeAg negative	confirmed HBsAg loss and anti-HBs seroconversion
Cirrhotics	confirmed HBsAg loss and anti-HBs seroconversion

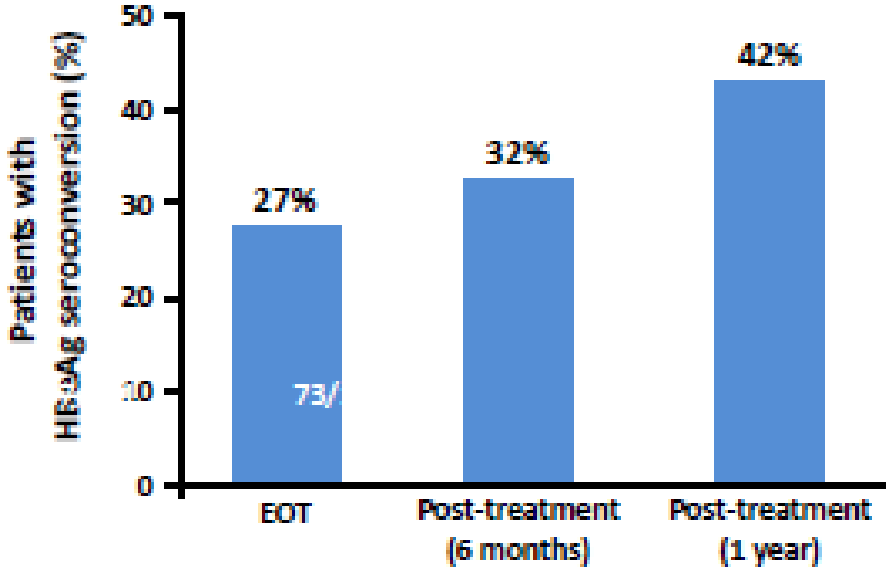
*A proportion of patients who **discontinue NUC** therapy after anti-HBe seroconversion may require retreatment, since they fail to sustain their serological and/or virological response

adapted from EASL HBV Guidelines, J Hepatol 2012

48 week peg-IFN alfa in chronic hepatitis B

HBeAg positive

Lau GKK, et al. N Engl J Med 2005; 352: 2682;
Lau GKK, et al. 41st EASL 2006: Abstract 50.

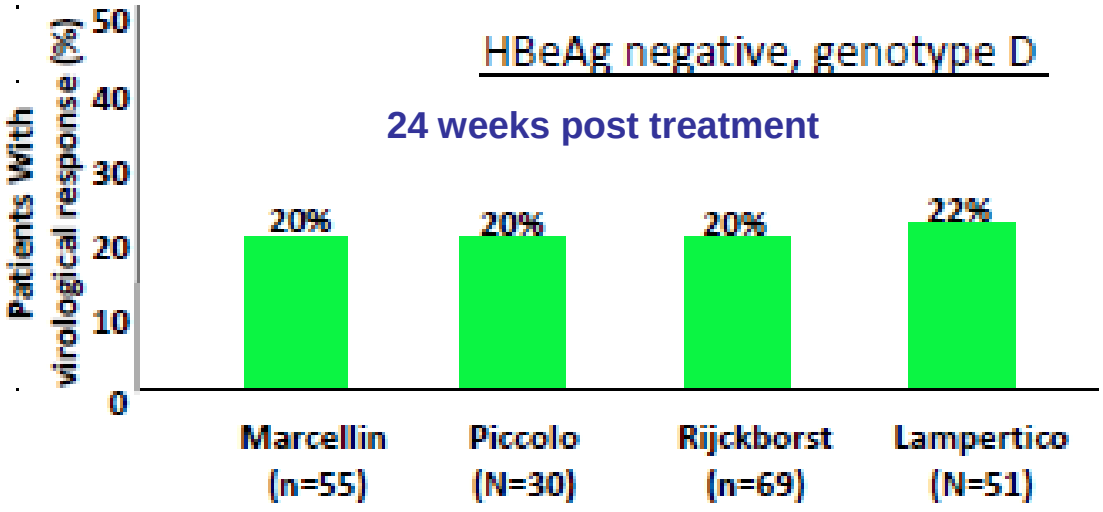


81% DOPO 6 ANNI

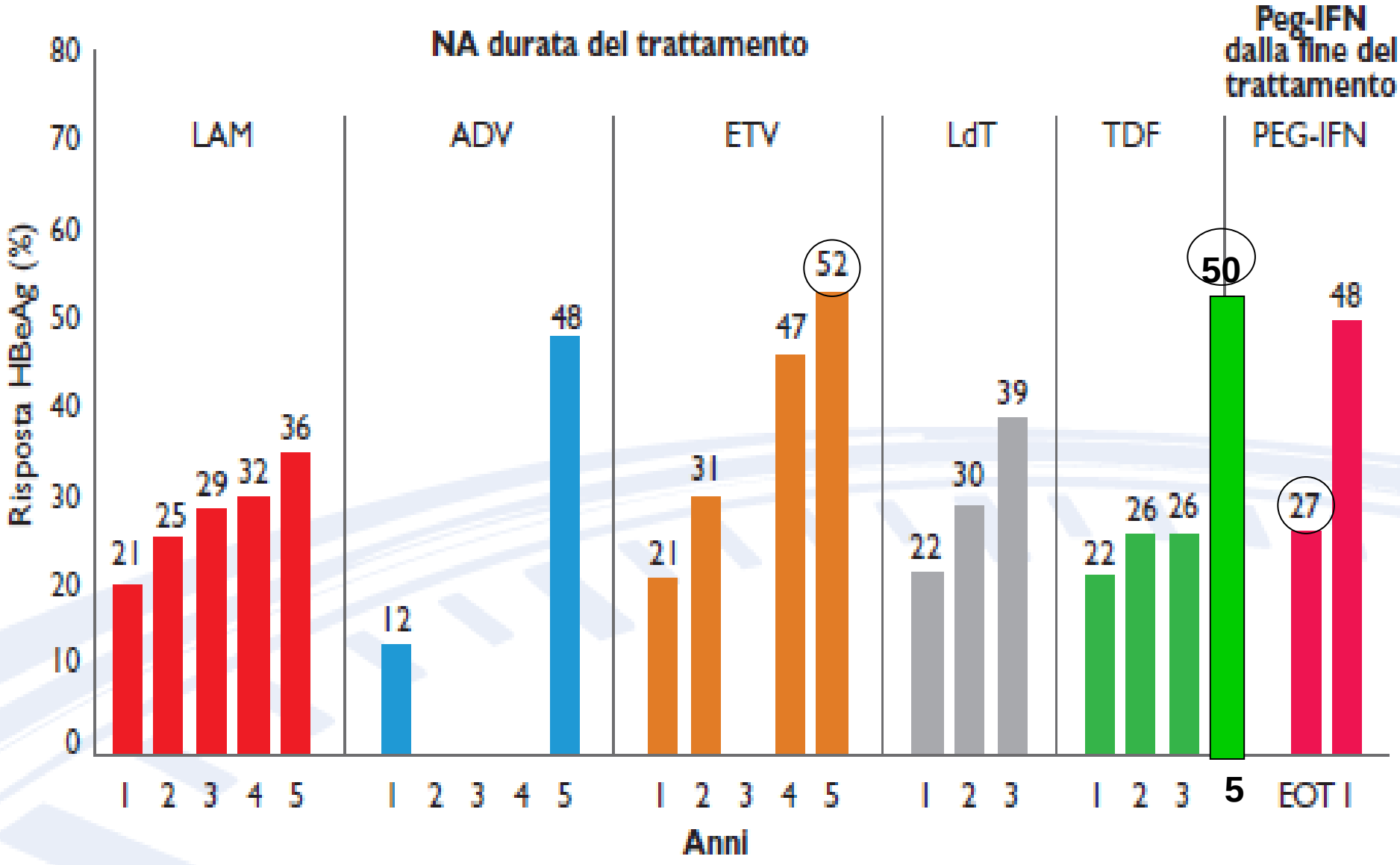
Buster et al. Gastroenterology 2008

HBeAg negative, genotype D

24 weeks post treatment



Terapia antivirale: clearance dell' Antigene e



Marcellin et.al; AASLD 2011 *Gish Gastroenterology 2007, Marcellin N Engl J Med 2003, Marcellin Hepatology 2008, Chang TT Hepatology 2010, Liaw Gastroenterolgy 2009, HSU J Hepatol 2009,, Heathcote AASLD 2009, Lau. NEJM 2005.*

EFFETTI COLLATERALI DELL' INTERFERONE

Febbre (Sindrome simil-influenzale)

Affaticamento *

Mialgia

Cefalea

Inappetenza/Anoressia *

Alopecia

Irritabilità

Depressione

Disturbi del sonno

* Più frequenti nella fibrosi avanzata

Piastrinopenia * e/ o leucopenia (neutropenia)

condizionano una riduzione della dose in circa il 40% dei pz. e la sospensione nel 10% dei casi. (maggiormente nei pz. con malattia avanzata ed ipersplenismo)

Aumento delle transaminasi sia durante che a fine terapia

EFFETTI COLLATERALI DEGLI NUC (S)

- Flares di ALT on treatment e off treatment
- Effetti collaterali aspecifici
- Effetti collaterali “di classe”
  - Carcinogenicità
  - Embriotossicità
  - **Tossicità mitocondriale dose dipendente**
    - Danno metabolico ed epatico: acidosi lattica ed epatomegalia steatosica
    - Danno d’organo: cellula target ← farmaco

Lamivudina: pancreas, muscolo → pancreatite e miopatia

Entecavir: non rilevante

Telbivudina: muscolo, neurone → miopatia e polineuropatia

Adefovir e Tenofovir: rene → nefropatia (S.di Fanconi)

ac. Metabolica,ipofosfatemia , glicosuria

Definizione di risposta

Terapia	Risposta	Definizione
NAs	**Non-risposta primaria**	Riduzione HBV DNA sierico <1$\log_{10}$ IU/mL dal baseline, **alla 12°settimana (3 mese di terapia)**
	Risposta Virologica	HBV DNA non rilevabile* entro 48 settimane di terapia **(HBV DNA < 200** alla 24° o 48° settimana)
	Risposta virologica parziale	Riduzione HBV DNA sierico >1$\log_{10}$ IU/mL dal baseline, ma ancora detectabile HBV DNA* **alla 24° o 48°settimana di terapia (6 mesi - 12 mesi). (HBV DNA > 2000 UI/ml)**
	breakthrough virologico	Incremento durante la terapia HBV DNA sierico >1$\log_{10}$ IU/mL rispetto il valore al nadir.
IFN-α	**Non-risposta primaria**	Riduzione HBV DNA sierico < 1 $\log_{10}$ IU/mL dal baseline, **alla 12°settimana (3 mese di terapia)**
	Risposta Virologica	HBV DNA <2000 IU/mL **alla 24 settimana di terapia (6 mesi).**
	Risposta Sierologica	HBe seroconversione nei pz. HBeAg(+)

* con real-time PCR.

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *J Hepatol*. 2009;50:227-42

Response-guided therapy (RGT) using HBsAg levels in Peg-IFN-treated patients: stopping rules*

HBeAg-positive	HBeAg-negative (geno D)
Week 12: - No decline of HBsAg - HBsAg >20,000 IU/mL	Week 12: -No decline in HBsAg + < 2 log decline in HBV DNA

*** 97-100% Negative Predictive Values**

La cinetica di riduzione dell' HBsAg sierico durante e a fine terapia, sembra essere un marker predittivo di SVR e clearance di HBsAg , nella valutazione della risposta *al trattamento con PEG IFN in pz. con ECA HBeAg negativo* (Brunetto MR. -Hepatology 2009; 49)

.

Il dosaggio combinato di HBsAg e HBV DNA raggiunge un potere predittivo elevato alla 12°settimana di te rapia : interruzione del trattamento in circa il 20% dei casi.

Sonneveld et al. Hepatology 2010
Piratvisuth et al. APASL 2010
Liaw et al. Hepatology 2011

Rijckborst et al. Hepatology 2010
Rijckborst / Lampertico et al. J Hepatol 2012

Unresolved issues and unmet needs

- **Improve knowledge and prognosis** of the natural history and indications for treatment, particularly in HBeAg-positive immunotolerant patients and HBeAg-negative patients with serum HBV DNA levels below 20,000 IU/ml.
- **Assess the role of non-invasive markers** (serum and biophysical) for the evaluation of the severity of liver disease and for the follow-up of treated and untreated patients.
- **Further clarify the role of serum HBsAg levels** in the evaluation of the natural history, prediction of therapeutic responses and treatment individualisation.
- **Assess host genetic and viral markers** to determine prognosis and optimise patients' management.
- Assess the impact of early diagnosis and early treatment intervention.

- **Assess long-term safety** and resistance to the current first line NAs (entecavir and tenofovir).
- **Identify markers that predict successful NA discontinuation.**
- **Assess the safety and efficacy of the combination of PEGIFN with a potent NA** (entecavir or tenofovir) to increase anti-HBe and anti-HBs seroconversion rates.
- Develop and assess new drugs and therapeutic approaches, particularly immunomodulatory therapies, to enhance loss of HBeAg and HBsAg and subsequent seroconversion.
- Assess long-term impact of therapy on the prevention of cirrhosis and its complications and HCC.
- Develop strategies and identify subgroups for effective HBIg free prophylaxis after liver transplantation for HBV related liver disease.

EASL HBV Guidelines J.Hepatology 2012

HEPATOLOGY
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HEPATOLOGY, December 2012

Targeted Delivery of Interferon-α to Hepatitis B Virus-Infected Cells Using T-Cell Receptor-Like Antibodies

Changhua Ji,[1] Konduru S.R. Sastry,[2] Georg Tiefenthaler,[3] Jennifer Cano,[1] Tenny Tang,[1] Zi Zong Ho,[2] Denise Teoh,[2] Sandhya Bohini,[1] Antony Chen,[2] Surya Sankuratri,[1] Paul A. Macary,[4] Patrick Kennedy,[5] Han Ma,[1] Stefan Ries,[3] Klaus Klumpp,[1] Erhard Kopetzki,[3] and Antonio Bertoletti[2,6,7]

Gastroenterology 2012 ;143 :963-97

CLINICAL—LIVER

Restored Function of HBV-Specific T Cells After Long-term Effective Therapy With Nucleos(t)ide Analogues

CAROLINA BONI,* DILETTA LACCABUE,* PIETRO LAMPERTICO,‡ TIZIANA GIUBERTI,* MAURO VIGANÒ,‡ SIMONA SCHIVAZAPPA,* ARIANNA ALFIERI,* MARCO PESCI,* GIOVANNI B. GAETA,§ GIUSEPPINA BRANCACCIO,§ MASSIMO COLOMBO,‡ GABRIELE MISSALE,* and CARLO FERRARI*

*Laboratory of Viral Immunopathology, Unit of Infectious Diseases and Hepatology, Azienda Ospedaliero-Universitaria di Parma, Parma; ‡First Division of Gastroenterology, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan; and §Divisione Epatiti Virali Acute e Croniche, II Università di Napoli, Naples, Italy

Gastroenterology 2012 ;143 : 1576-1585

Combined Blockade of Programmed Death-1 and Activation of CD137 Increase Responses of Human Liver T Cells Against HBV, But Not HCV

PAOLA FISICARO,* CATERINA VALDATTA,* MARCO MASSARI,‡ ELISABETTA LOGGI,§ LARA RAVANETTI,* SIMONA URBANI,* TIZIANA GIUBERTI,* ALBERTINA CAVALLI,* CARMEN VANDELLI,‖ PIETRO ANDREONE,§ GABRIELE MISSALE,* and CARLO FERRARI*

*Laboratory of Viral Immunopathology, Unit of Infectious Diseases and Hepatology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; ‡Unit of Infectious Diseases, IRCCS "Tecnologie Avanzate e Modelli Assistenziali in Oncologia", Arcispedale S. Maria Nuova of Reggio Emilia, Reggio Emilia, Italy; §Department of Clinic Medicine, Laboratory of Cellular Immunology, University of Bologna, Bologna, Italy; ‖Dipartimento Integrato di Medicina e di Specialità Mediche, University of Moden and Reggio Emilia, Modena, Italy

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