

Assessment of both virologic response at week 4 and at week 12 optimizes prediction of treatment outcome in patients with chronic hepatitis C treated with peginterferon alfa-2b plus ribavirin.

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Background

Recently, it has been reported that both:

- Baseline viral load below 400 000 IU/ml**
- Rapid serum HCV RNA decrease after treatment initiation**

are important factors for Sustained Virologic Response achievement in patients treated with peginterferon (PEG-IFN) + ribavirin.

Objective of the study

- **Provide an early prediction regarding Sustained Virologic Response, in a community based study of patients treated with combination therapy, including naive or non-responders to previous therapy.**
 - **Prediction was assessed :**

| | |
|-----------------|---|
| Baseline | Initial viral load level |
| Week 4 | Rapid Virologic Response (RVR) |
| Week 12 | non-Early Virologic Response (non-EVR) |
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Patients

408 patients with chronic Hepatitis C, consecutively referred to our center

- 221 naives**
- 62 relapsers**
- 125 non-responders**

All the patients had

- serum ALT > Upper limit of normal**
- Histological proven CHC (liver biopsy).**

None was infected with HBV or HIV.

Treatment Schedules

All the patients underwent combination therapy

Pegylated interferon α 2b, 1.5 μ g/ kg/week

**Ribavirin, 1000-1200 mg according to weight
(less or more than 75 kg)**

Duration of treatment

- 24 weeks in naive patients genotype 2 or 3**
 - 48 weeks in naive patients genotype 1 or 4
in previously treated patients**
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HCV RNA testing

Quantitative detection

**VERSANT HCV 3.0 assay (bDNA) (Siemens)
(sensitivity 615 IU/ml, 3200 copies/ml).**

Qualitative detection

**VERSANT HCV Qualitative assay (TMA)
(Siemens)(sensitivity 9.6 IU/ml, 50 copies/ml).**

**Serum samples were tested at :
baseline, weeks 4, 12, end of treatment, and
end of follow-up (24 weeks).**

Models

Univariate Analysis

Positive Predictive Value (PPV)

| | |
|---------------------|----------------------------------|
| Baseline Viral Load | \leq vs $>$ 400 000 IU/ml |
| Week 4 (RVR) | Undetectable TMA |
| | ≥ 2 log decrease initial VL |

Negative Predictive Value (NPV)

| | |
|-------------------|-------------------------------|
| Week 12 (non-EVR) | Detectable TMA |
| | $<$ 2 log decrease initial VL |

Multivariate Analysis

Identify characteristics independently associated with Rapid Virologic Response (Week 4)

Multivariate analysis

Factors

Comparison

Gender

Female vs male

Age

≤ 45 years vs > 45 years

ALT

$\leq 2 N$ vs $> 2 N$

Initial Viral Load

$\leq 400\ 000$ vs $> 400\ 000$ IU/ml

Genotype

1, 4, 5, 6 vs 2 and 3

Liver Histology

**Activity grade
Fibrosis stage**

Status

Naive vs Relapser vs non-Responder

Patients Characteristics

| | Naive (n=221) | RR (n=62) | NR (n=125) |
|----------------------------|-------------------------|---------------------|----------------------|
| Male | 67 % | 66 % | 73% |
| Age* | 47 ± 10 | 49 ± 10 | 51 ± 10 |
| < 45 years | 52 % | 35 % | 33 % |
| ALT (IU/ml)* | 113 ± 76 | 112 ± 91 | 155 ± 91 |
| Source of Infection | | | |
| Blood Transfusion | 26 % | 25 % | 41 % |
| IV Drug Use | 36 % | 41 % | 19 % |
| Sporadic | 38 % | 34 % | 40 % |

* Mean ± SD

** previous therapy

Patients characteristics

| | Naive (n=221) | RR (n=62) | NR (n=125) |
|--------------------|-------------------------|---------------------|----------------------|
| Activity* | | | |
| 1-2 | 99 % | 95 % | 90 % |
| > 2 | 1 % | 5 % | 10 % |
| Fibrosis* | | | |
| ≤ 2 | 68 % | 68 % | 47 % |
| 3 | 19 % | 17 % | 25 % |
| 4 | 13 % | 15 % | 28 % |
| Treatment** | | | |
| IFN | - | 38% | 57% |
| IFN+Riba | - | 49% | 41% |
| PEG-IFN+Riba | - | 13% | 2% |

*METAVIR scoring system **previous therapy

Patients Characteristics

| | Naive (n=221) | RR (n=62) | NR (n=125) |
|--------------------|-------------------------|---------------------|----------------------|
| Genotype | | | |
| 1a | 22 % | 19 % | 20 % |
| 1b | 31 % | 34 % | 50 % |
| 2-3 | 37 % | 43 % | 16 % |
| 4-5 | 10 % | 4 % | 14 % |
| Viral load* | 5.52 ± 0.68 | 5.60 ± 0.69 | 5.65 ± 0.65 |
| ≤ 400 000** | 51 % | 47 % | 42 % |

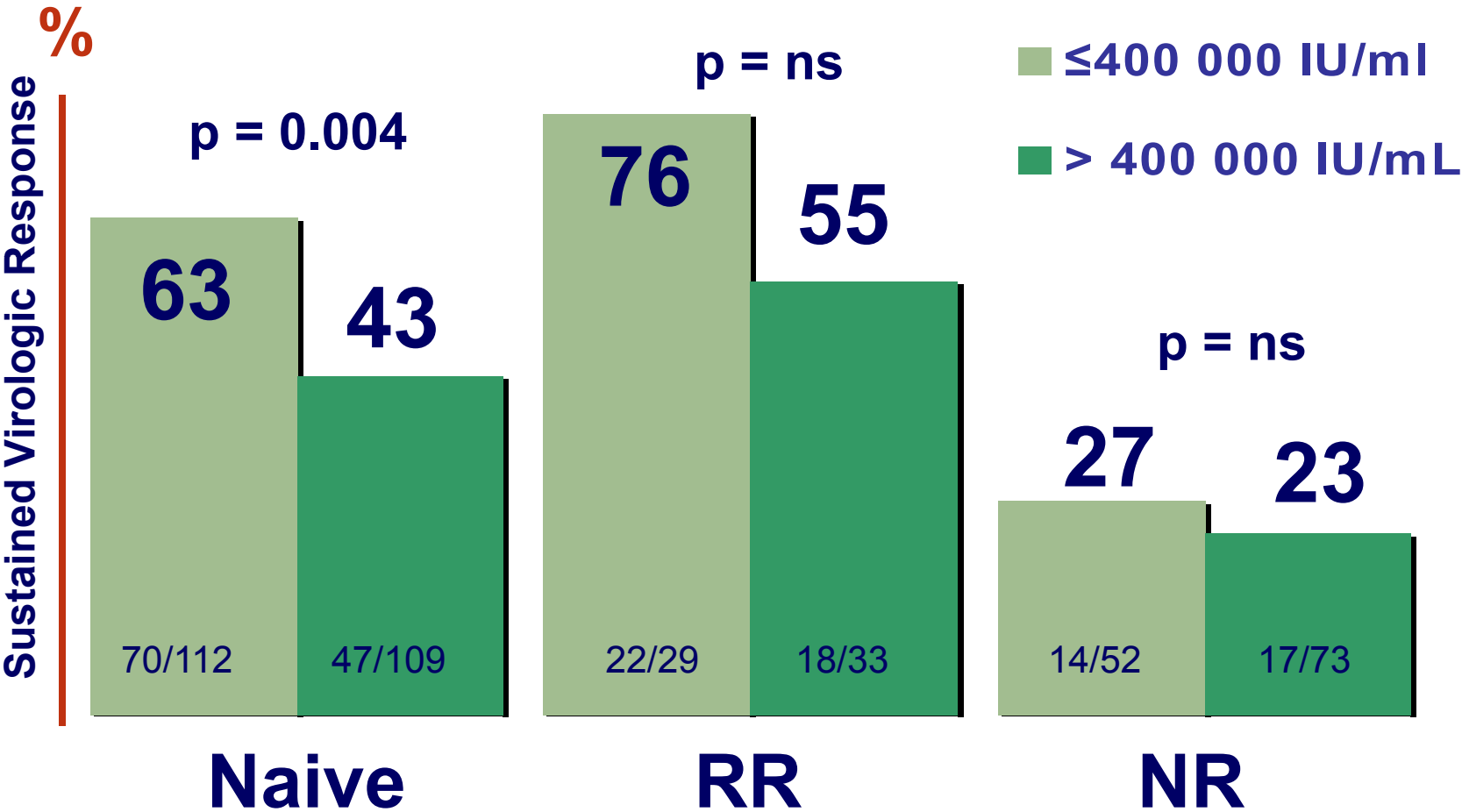
*log IU /ml Mean±SD ** IU/ml

Response to treatment

| | Naive (n=221) | RR* (n=62) | NR* (n=125) |
|---------------------|--------------------------------|-----------------------------|------------------------------|
| SVR | 53 % | 65 % | 25 % |
| Relapse | 11 % | 19 % | 57 % |
| Non-Response | 36 % | 16 % | 18 % |

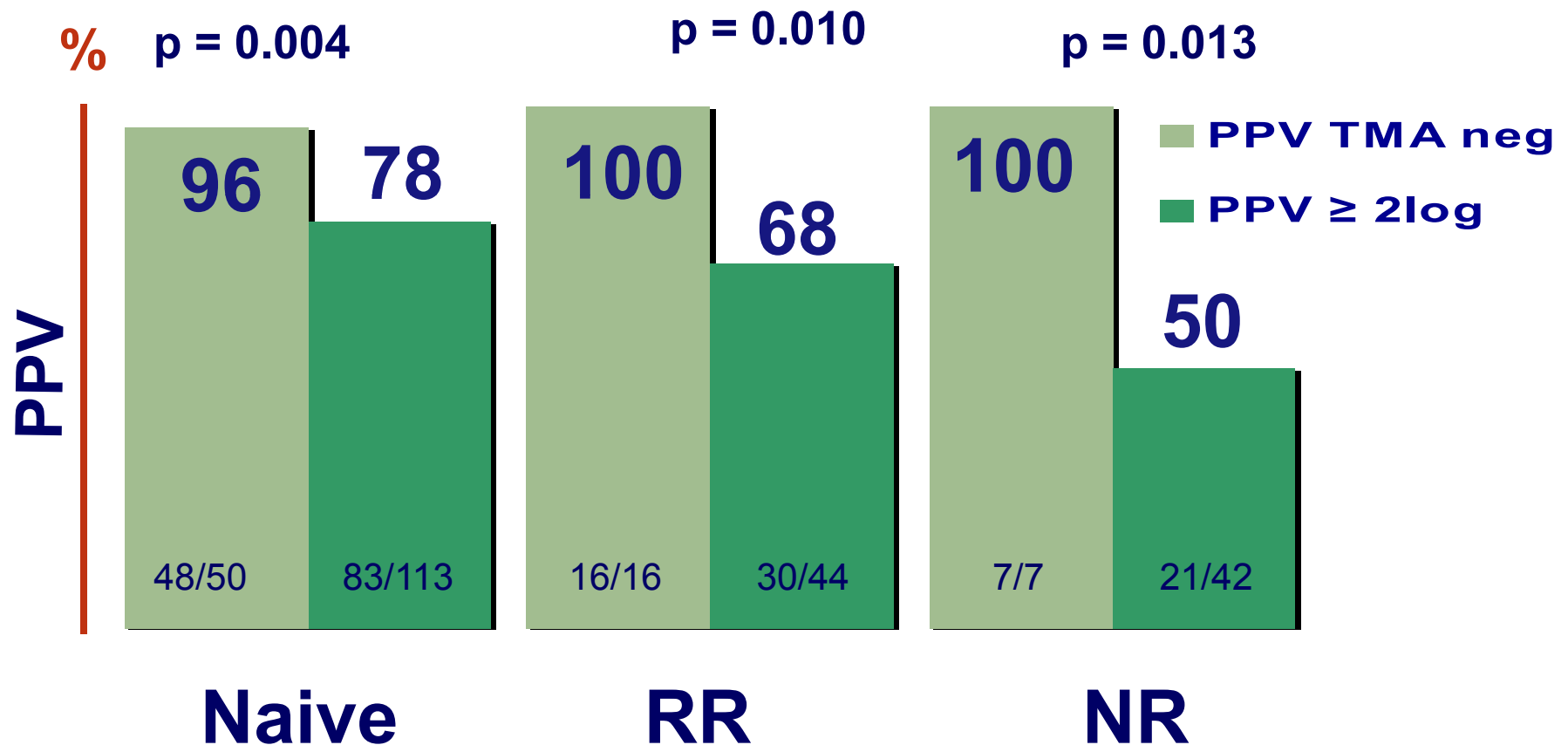
* To previous therapy

Predictive value of Initial Viral Load



Week 4: Rapid Virologic Response

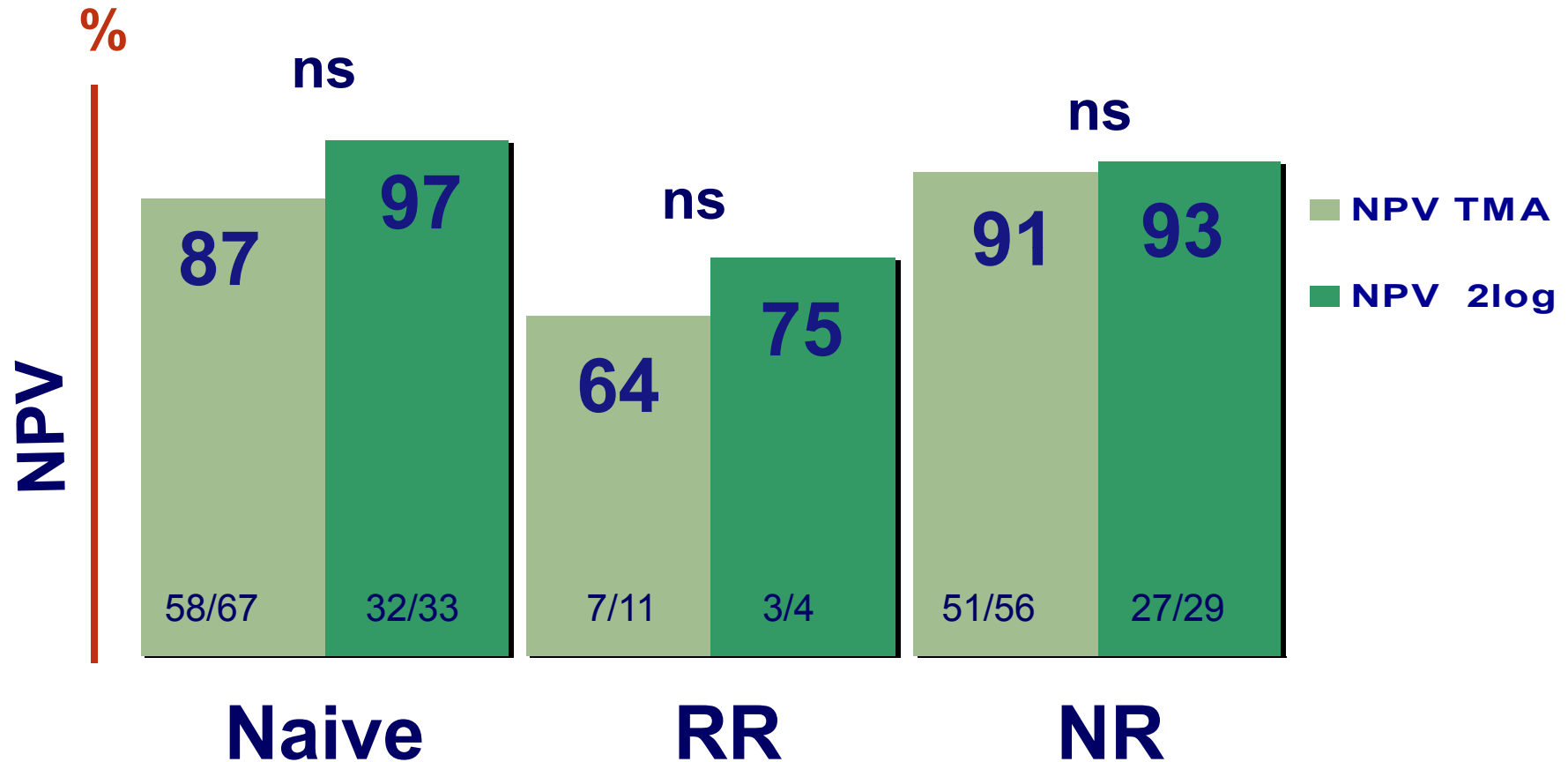
Undetectable TMA or ≥ 2 log Decrease



Specificity : TMA: 76%, 61%, 68%; 2 log drop: 46%, 18%, 46%

Week 12: non-Early Virologic Response

detectable TMA or < 2 log decrease



Specificity : TMA: 75%, 73%, 64%; 2 log drop: 82%, 80%, 74%

Univariate Analysis

| | Patients with RVR* | | p |
|---------------------------------|--------------------|---------|----------|
| Age \leq vs $>$ 45 years | 29 % | 16 % | $<.008$ |
| Genotype 2-3 vs 1-4 | 43% | 10 % | $<.0001$ |
| BVL \leq vs $>$ 400 000 IU/ml | 32 % | 13 % | $<.0001$ |
| Fibrosis stage ** | 29%-25 % | 17%-9 % | 0.005 |
| Patients status | | | |
| Naive+RR vs NR | 27%-31 % | 7 % | $<.0001$ |

* TMA undetectable at week 4

** METAVIR score analyzed continuously

Multivariate Analysis

Factors independently associated with RVR

| | OR | 95% CI | p |
|--------------------------------------|-------------|--------------------|-------------------|
| Genotype 2-3 | 6.84 | 3.60 - 13.0 | < .0001 |
| VL \leq 400 000* | 3.61 | 1.90 - 6.85 | < .0001 |
| Status** | 3.14 | 1.27 - 5.79 | 0.013 |
| Fibrosis stage*** | 1.48 | 1.07 - 2.03 | 0.016 |

* IU/ml ** Naive or Relapser *** METAVIR score analyzed continuously

Conclusions

In routine patients receiving PEG-IFN + RBV therapy:

- A **Rapid Virologic Response** (undetectable TMA at week 4) is the **strongest predictor** (PPV 96% to 100%) of **Sustained Virologic Response**.
 - The **absence of Early Virologic Response** (< 2 log decrease of initial viral load at week 12) is the **strongest predictor** (NPV 75% to 97%) of **non response to therapy**.
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Conclusions

A Rapid Virologic Response is significantly and independently associated with:

- HCV Genotype 2 and 3**
 - Initial viral load $\leq 400\ 000$ IU/ml**
 - Fibrosis stage ≤ 2**
 - Patient status (naive or relapser)**
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Conclusions

Algorithm for viral testing to identify patients with RVR or non-EVR should include:

- **Baseline**
Quantitative HCV RNA testing
 - **Week 4**
Qualitative HCV RNA testing
to predict SVR
 - **Week 12**
Quantitative HCV RNA testing
to predict non-SVR
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