The Treatment of Hepatitis C
- State of the Art -

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Medical School of Hannover
Department of Gastroenterology, Hepatology and Endocrinology
Discovery of HCV in 1989

Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989

1. M. Houghton
2. Q-L Choo
3. G. Kuo
4. D. Bradley

HEPATITIS C

• After infection 50 – 80 % develop chronicity

• Worldwide 170 Million chronic hepatitis C patients

• Main cause for hepatocellular carcinoma (HCC) + liver transplantation in „the Western world“

• Incidence for HCC and liver cirrhosis increasing
HCV: 6 Major Genotypes
Diagnostics: ultra sensitive PCR methods are requisite

- **Prognostic Threshold**
  - 800,000 IU/ml
  - Roche Cobas HCV 2.0
  - Bayer Versant HCV 3.0
  - LCx HCV RNA Quantitative
  - CDx HCV RNA Quantitative
  - Roche Cobas TaqMan HCV

- **Sustained Viral Response**
  - 50 IU/ml
  - Roche Qual
  - TMA Qual
  - 10 IU/ml
  - 1 IU/ml

- **Diagnostics:**
  - ultra sensitive PCR methods are requisite
Rationale to treat acute HCV infection

10-50% Resolution

50-90% Chronic Hepatitis C

Early treatment
HEP-NET Acute HCV-I Study

24 weeks IFN alpha-2b monotherapy (first 4 weeks daily 5MU)

Santantonio et al. (Bari, Italy)

Jaeckel et al., NEJM 2001
HEP-NET Acute HCV-III Study

asymptomatische Patienten

Randomization 1:1

Symptoms 4 weeks

1.5 μg/kg Peg-IFNa-2b 24 weeks

HCV-RNA pos

12 weeks observation

HCV-RNA neg

PEG-IFNa-2b 1,5 μg/kg Ribavirin > 10.6 mg/kg 24 weeks

FOLLOW UP

HCV-RNA positive

PEG-IFNa-2b 1,5 μg/kg Ribavirin > 10.6 mg/kg 24 weeks

Recruitment >95 patients
HEPATITIS C - Milestones

- Discovery of HCV (1989)
- First usage of IFN alpha in nonA, nonB hepatitis
Chronic Hepatitis C: Improvement by trial and error

Sustained virological response

Optimization of dose and duration

- IFN 24 weeks
- IFN 48 weeks

Chronic Hepatitis C: Improvement by trial and error

Sustained virological response

One unspecific drug plus another unspecific drug = highly effective therapy

IFN 24 weeks

IFN 48 weeks

IFN & Ribavirin 48 weeks


80%

60%

40%

20%

0%
>50% cure of chronic Hepatitis C

Sustained virological response

- **IFN & Ribavirin**: 48 weeks
- **PEG-IFN & Ribavirin**: 40 kDa PEG-IFN alfa-2a, 12 kDa PEG-IFN alfa-2b
- **PEG-IFN 48 weeks**: 2001

Graph showing increasing percentage of sustained virological response from 1988 to 2001.
More than 50% of patients with chronic hepatitis C can be cured

**Sustained Response**

**PEG-IFN alfa-2b**

Manns et al., *Lancet* 2001

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN + RBV</td>
<td>47%</td>
<td>n = 505</td>
</tr>
<tr>
<td>0.6 PEG-IFN + RBV</td>
<td>47%</td>
<td>n = 514</td>
</tr>
<tr>
<td>1.5 PEG-IFN + RBV</td>
<td>54%</td>
<td>n = 511</td>
</tr>
<tr>
<td>1.2 g RBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.8 g RBV</td>
<td></td>
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</tbody>
</table>

**Sustained Response**

**PEG-IFN alfa-2a**

Fried et al., *NEJM* 2002

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN + RBV</td>
<td>45%</td>
<td>n = 444</td>
</tr>
<tr>
<td>PEG-IFN + P</td>
<td>30%</td>
<td>n = 224</td>
</tr>
<tr>
<td>PEG-IFN + RBV</td>
<td>56%</td>
<td>n = 453</td>
</tr>
</tbody>
</table>
PEG-IFN alpha-2b & Ribavirin

Manns et al., Lancet 2001

% of patients

- Genotype 1
- Genotypes 2/3

3MIU + RBV
- 33%

Peg 1.5/0.5 µg/kg + RBV
- 79%

Peg 1.5 µg/kg + RBV (1000/1200 mg)
- 80%

Peg 1.5 µg/kg + RBV (800 mg)
- 82%
Chronic Hepatitis C:

- PEG-Interferon alpha2a (Pegasys) (180µg)
- PEG-Interferon alpha2b (PegIntron) (1,5µg/kg)
  +
  Ribavirin 800-1200 (1400) mg

Genotyp 1/4: 48 Weeks
Genotyp 2/3: 24 Weeks

Genotype 1: Stop of Therapy at Week 12
if not 2-log decrease in HCV-RNA
Chronic Hepatitis C a Curable Disease:

SVR 24 IS CURE !!!!!!!!

Five Year Longterm Follow Up:

McHutchison et al, EASL 2006
  IFN, IFN + Riba

Swain et al, EASL 2007
  PEG-IFN alpha2a, PEG-IFN alpha2a + Riba

Manns et al, EASL 2008
  PEG-IFN alpha2b, PEG-IFN alpha2b + Riba
IDEAL-Study: Design

3,070 previously untreated U.S. patients with HCV genotype 1
48 weeks of treatment

PEGINTRON (PEG-IFN alpha 2b) 1.5 mcg/kg/week
REBETOL (Ribavirin) 800-1,400 mg/day

PEGINTRON 1.0 mcg/kg/week
REBETOL 800-1,400 mg/day; and

Pegasys (PEG-IFN alpha 2a) 180 mcg/week
Copegus (Ribavirin) 1,000-1,200 mg/day

McHutchison et al, EASL, 2008
IDEAL-Study: Results

![Graph showing sustained virological response percentages for different treatments.]

**PEG-IFNa-2b 1.5 µg/kg**
- RBV 800-1400
- 40 %

**PEG-IFNa-2b 1.0 µg/kg**
- RBV 800-1400
- 38 %

**PEG-IFNa-2a**
- RBV 1000/1200
- 41 %

*Sustained Virological Response [%]*

Schering-Plough Press Release Jan 14 2008

McHutchison et al, EASL, 2008
Treatment of HCV disease is evolving

Patients achieving SVR (%)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>IFN monotherapy</th>
<th>Peg-IFN</th>
<th>IFN + ribavirin</th>
<th>Peg-IFN + ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>6-19</td>
<td>18-39</td>
<td>61-79</td>
<td>76-82</td>
</tr>
<tr>
<td>48</td>
<td>11-19</td>
<td>35-43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>10-22</td>
<td>33-36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg-IFN</td>
<td>42-46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN + ribavirin</td>
<td>42-46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peg-IFN + ribavirin</td>
<td>76-82</td>
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</table>

*Range of values reported; lower bar represents lower value;

Approaches to Improve the Treatment for HCV

- Tailoring therapy with existing drugs
  - Ribavirin Analogue
  - Taribavirin

- Improving existing drugs
  - New IFNs
  - AlbIFN etc.

- STAT-C drugs
  - VX950
  - SCH 503034
  - R1626
  - Etc.
Factors associated with sustained virological response = clinical cure

- HCV-Genotype (tailoring before therapy), Viral Load
- Kinetics of HCV-RNA during early treatment (tailoring during therapy)

HCV-RNA analysis at week 4 and 12 are crucial in order to tailor treatment of HCV
Shorter Therapy in Rapid Virological Responders (RVR) (Week 4 HCV-RNA negative)

**Week 4: HCV-RNA negative**

**Genotype 1:**
24 week therapy if low pretreatment viral load

*PEG-IFNa-2b + Ribavirin: Zeuzem et al., J Hepatol 2005*

*PEG-IFNa-2a + Ribavirin: Ferenci et al*

**Genotype 2/3:**
12-16 Week Therapy

*Mangia et al., NEJM 2005 (12 Weeks)*

*Dalgaard et al., Nordic-C Study EASL 2007 (14 Weeks)*

*v. Wagner et al., Gastroenterology 2005 (16 Weeks)*
Prolongation of Therapy in “Slow-Responders”

Wo 12: > 2 log HCV RNA Reduction but TMA pos (109/455)

Week 24: 24% HCV RNA negative (< 50 IU/ml) (26/109)

48 Weeks Therapy
- Relapse rate: 87%

72 Weeks Therapy
- Relapse rate: 46%

(Berg T et al. Gastroenterology 2006)
Individualized Therapy in Chronic Hepatitis C

- Genotype 2+3: 24 (12-48) weeks
- Genotype 4: 48 weeks
- Genotype 5 +6: (24-) 48 weeks
- Genotype 1: 24-48 (72) weeks
The Future: New drugs

- Ribozymes
- Antisense Nucleotides
- HCV protease Inhibitors
- HCV polymerase Inhibitors
- Glucosidase Inhibitors
- Entry Inhibitors

Interaction with the Host
- TLR-agonists
- Therapeutic vaccination
- Interferons

Adapted from: Pawlotsky et al., Antivir Ther 2006
Targeting HCV RNA-dependent RNA polymerase and NS3/4A protease

Different allosteric sites for nonnucleoside inhibitors (fingertip-thumb site)

Catalytic site: nucleoside analogs converted to nucleotides leading to chain termination

Protease inhibitors

NS4A Cofactor

S282

P495

M414

M423

L419
HCV-Protease Inhibitor: Proof of Concept


**BILN-2061**
in HCV-genotype 1¹

**BILN-2061**
in HCV-genotype 2/3²
Inhibition of IFN induction and effector phase by HCV proteins (NS3/4A)

Li et al., PNAS 2005; Meylan et al., Nature 2005
Inhibition of NS3/4A may restore IFN pathway
# New Therapies for Hepatitis C

## Viral entry inhibitors
- Hepatitis C immunoglobulin (HClg)
- HCV-Ab 68 and Ab 65 (monoclonal Ab)

## HCV RNA translation inhibitors
- ISIS 14803 (antisense)
- AVI – 4065 (antisense)
- Heptazyme (ribozyme)
- VGX-410C (small molecule IRES inhibitor)
- TT 033 (siRNA)

## Posttranslational processing inhibitors
- **NS3-4A serine protease inhibitors**
  - BILN 2061
  - ITMN 191
  - VX-950
  - SCH 503034
  - ACH-806/GS-9132

## Phase of development
- Preclinical
- I
- II
- III
- IV

### Development halted
- * Development halted

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Modified from Pawlotsky JM et al. Gastroenterology 2007
New Therapies for Hepatitis C

HCV replication inhibitors

**NS5B polymerase inhibitors**
- MK-0608
- HCV-796
- R1626
- JTK-003
- NM283
- XTL 2125

**Cyclophilin B inhibitors**
- DEBIO-025
- NIM-811

**NS5A inhibitors**
- A-831, A-689

**Helicase inhibitors**
- QU663
- Recombinant Ab fragments

Virus assembly and release inhibitors
- UT-231B (iminosugar-glucosidase inhibitor)
- Celgosivir (glucosidase inhibitor)

Toll Like Receptor Agonists
- CPG10101
- ANA975

**Phase of development**

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
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<tbody>
<tr>
<td>*</td>
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</table>

* Development halted

Adapted from Pawlotsky JM et al. Gastroenterology 2007
Telaprevir VX-950 (Vertex)
Fast Development of Resistance

Reesink et al., Gastroenterology 2006
Identified mutations which confer resistance to small-molecule antivirals

NS3 serine protease (green) and central domain of NS4A (red)

NS5B RNA-dependent RNA polymerase (thumb, palm and fingers domains are blue, green and red, respectively)

NNI, non-nucleoside inhibitor; NA, nucleoside analogue

De Francesco R et al. Nature 2005
Problem: Development of resistance

- HCV replication creates sequence diversity in viral genomes generating a population of viral quasispecies
  - High levels of HCV replication
  - Error prone RNA-dependent RNA polymerase

<table>
<thead>
<tr>
<th>Resistant mutants against HCV protease Inhibitors isolated in vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td>BILN 2061&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>A156V/T R155Q D168A/V/Y</td>
</tr>
</tbody>
</table>

Sensitive to PEG-IFN
Kieffer et al., 2006
### Telaprevir PROVE2 SVR Rates

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Arm N=82</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>24 Week Arm n=81</td>
<td>SVR12</td>
<td>65%</td>
</tr>
<tr>
<td>12 Week Arm n=82</td>
<td>SVR24*</td>
<td>59%</td>
</tr>
<tr>
<td>No RBV Arm n=78</td>
<td>SVR24**</td>
<td>29%</td>
</tr>
</tbody>
</table>

* No relapse between SVR 12 and 24
** One relapse between SVR 12 and 24

Hezode et al, AASLD 2007

Intent-To-Treat Analysis
WHAT WILL WE ACHIEVE WITH THE NEW ANTI HCV DRUGS (STAT-C) ?

- Triple therapy (PEG-IFN + RIBA + anti HCV drug)
- Slightly higher SVR in naive genotype 1 patients
- Shorter duration of treatment: 24 weeks
- Additional toxicity
- Additional Cost
- Not before 2011
# LIMITATIONS OF NEW ANTI HCV DRUGS

- Resistance
- Toxicity
- Cost
- Pharmacokinetic profile
- Benefit for non-responders ???
### Naive patients ("Sprint-1 Study"; n=595): Week 12 response (<15 IU/ml)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-Intron + RBV 800-1400 + Boceprevir 800 mg</td>
<td>70%</td>
</tr>
<tr>
<td>Peg-Intron + RBV 800-1400 + Boceprevir 800 mg (started at week 5)</td>
<td>79%</td>
</tr>
<tr>
<td>Peg-Intron + RBV 400-1000 + Boceprevir 800 mg</td>
<td>54%</td>
</tr>
<tr>
<td>Peg-Intron + RBV 800/1400 (Standard of Care)</td>
<td>34%</td>
</tr>
</tbody>
</table>

### Nonresponder patients: Sustained Virological Response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-Intron +/- RBV 800-1400 + Boceprevir (100- 800 mg)</td>
<td>7-14%</td>
</tr>
</tbody>
</table>

*Change of protocol during treatment:

- *Boceprevir dose was increased from lower doses to 800mg in pts. with antiviral response*

| Peg-Intron + RBV 800/1400 (Standard of Care)      | 2%       |

Schiff et al, EASL 2008
Development of further IFNs

- Alb-Interferon (Novartis) - Phase III
  - Albumin Interferon alpha-2b → longer half life
- BLX883 - Locterion (Biolex, Octoplus) Phase II
  - New release system
- Omega (Biomedicines) IFN Phase II
  - Implantable infusion pump
- Belerofon (Nautilus Biotech) - Phase I
  - Oral administration
- R7025 - MAXY-alpha (Maxygen, Roche) – Phase I
  - 50x greater in-vitro activity compared to PEG-IFN alpha-2a
Alb-Interferon – allows injection every 14 days.

Phase III studies are ongoing – Approval 2010?
Virological response (ITT analysis)

Response rate (%)

- PEG-IFN 180 µg Q1w (n=114)
- alb-IFN 900 µg Q2w (n=118)
- alb-IFN 1200 µg Q2w (n=110)
- alb-IFN 1200 µg Q4w (n=116)

- RVR4 (<LOQ)
- Week 12 (<LOQ)
- ETR (<LOD)
- SVR

- PEG-IFN 180 µg Q1w (n=114):
  - RVR4: 26%
  - Week 12: 66%
  - ETR: 53%
  - SVR: 26%

- Alb-IFN 900 µg Q2w (n=118):
  - RVR4: 34%
  - Week 12: 69%
  - ETR: 75%
  - SVR: 55%

- Alb-IFN 1200 µg Q2w (n=110):
  - RVR4: 25%
  - Week 12: 69%
  - ETR: 73%
  - SVR: 58%

- Alb-IFN 1200 µg Q4w (n=116):
  - RVR4: 18%
  - Week 12: 53%
  - ETR: 70%
  - SVR: 51%
Omega Interferon + DUROS® Device

- Implantable osmotic mini-pump
- Steady-state delivery of biologics for up to 12 months
- Quarterly dosing (4 implants/year)
- Insertion/removal in a 10- to 15-minute in-office procedure
We have a treatment for:

- Acute HCV
- Chronic GT 2 and 3 with RVR
- Chronic GT 1 low viral Load and RVR
Future HCV Treatment Paradigms

- Why do we need new treatments?
  - Improvement of SVR
    - Genotype 1
    - Difficult to treat populations
Reported SVR rates following treatment with pegIFNα and RBV in difficult-to-treat populations

SVR rate (%)

- **HIV coinfectedd**
  - Genotypes 1 or 4: 17–29*
  - Genotypes 2, 3 or 5: 6–28*

- **Africander Americans**
  - Genotypes 1 or 4: 44–62*
  - Genotypes 2, 3 or 5: 50

- **Steatosis**
  - Genotypes 1 or 4: 23
  - Genotypes 2, 3 or 5: 42

- **Advanced fibrosis / cirrhosisd**
  - Genotypes 1 or 4: 35
  - Genotypes 2, 3 or 5: 39

- **Liver transplant**
  - Genotypes 1 or 4: 31
  - Genotypes 2, 3 or 5: 60

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*Range of values reported; bar represents higher value*
Future HCV Treatment Paradigms

• Why do we need new treatments?
  – Improvement of SVR
  – Reduction of adverse effects
  – Reduction of treatment duration
  – Reduction of cost
  – Efficacy in Non-responders to PEG-IFN + Ribavirin
Global eradication of hepatitis C is achieved!
**In vitro** combination studies presented at EASL 2007 support concept of combination therapy with complementary modes of action

<table>
<thead>
<tr>
<th>Polymerase inhibitors (NS5B)</th>
<th>Protease inhibitors (NS3)</th>
<th>Other MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NM107*</td>
<td>Boceprevir</td>
<td>NIM811</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(cyclophilin inhibitor)</td>
</tr>
<tr>
<td>NM107*</td>
<td>Telaprevir</td>
<td>ACH806</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NS4A antagonist)</td>
</tr>
<tr>
<td>HCV-796</td>
<td>Boceprevir</td>
<td></td>
</tr>
<tr>
<td>R1479**</td>
<td>ITMN-191</td>
<td></td>
</tr>
<tr>
<td>R1479**</td>
<td>Telaprevir</td>
<td></td>
</tr>
</tbody>
</table>

**Results**

- Additive-to-synergistic antiviral efficacy
- Decreased emergence of resistant variants

*Ralston R et al; Lin K et al; Huang M et al; Howe AY et al; Seiwert SD et al; McCown M et al. EASL 2007*

*NM283; **R1626*
Identified mutations which confer resistance to small-molecule antivirals

De Francesco R et al. Nature 2005
UNMET NEEDS AND FUTURE PERSPECTIVES IN HCV THERAPIES

• All oral combinations

• Effective therapies for non-responders to PEG-IFN plus Ribavirin

• Prevention of Reinfection after OLT

• Prophylactic Vaccine?
Future concept of anti-HCV therapy

- Type-1 Interferon
  - HCV-protease inhibitors
    - Inhibition of replicase formation
  - HCV-polymerase inhibitors
    - Inhibition of Cyclophilin B
  - Ribavirin / ribavirin-like molecules (?)
  - TLR-agonists
  - Therapeutic vaccines
  - Entry Inhibitors
  - Release Inhibitors

Ritonavir (boosting)

Diagnostics:
ultra sensitive PCR methods are requisite

<table>
<thead>
<tr>
<th>Method</th>
<th>HCV RNA IU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMA</td>
<td>10</td>
</tr>
<tr>
<td>qual. PCR</td>
<td>100</td>
</tr>
<tr>
<td>quant. PCR</td>
<td>600</td>
</tr>
</tbody>
</table>
HEPATITIS C - Milestones

- Discovery of HCV (1989)
- Ribavirin
- Early IFN in acute HCV prevents chronicity
- 2007
- First usage of IFN alpha in nonA, nonB hepatitis
- Optimization of IFN treatment (duration, dosing)
- Other IFNs: IFN gamma, IFN beta, Lymphoblastoid IFN, Consensus IFN
PRESENT
Inhibition of IFN induction and effector phase by HCV proteins (NS3/4A)

Li et al., PNAS 2005; Meylan et al., Nature 2005
Present: Individualization of IFN therapy

- **HCV-G1, slow responder**
- **HCV-G1 HVL fast responder, HCV-G4 HVL**
- **HCV-G4, HCV-G3 HVL and slow responder**
- **HCV-G1 LVL fast responder, HCV-G2 slow responder**
- **HCV-G3 LVL fast responder**
- **HCV-G2 fast responder**

0 12 24 36 48 60 72

**Treatment Duration**

_HCV-G5 and HCV-G6: According to HCV-G4_
Discovery of HCV (1989)

First usage of IFN alpha in nonA, nonB hepatitis

Optimization of IFN treatment (duration, dosing)

Consensus interferon

Early IFN in acute HCV prevents chronicity

Pegylated IFN

Host factors TLR agonists therapeutic vaccines new interferons

Ribavirin

Small molecules i.e. proteas inhibitors

Optimization of IFN treatment (duration, dosing)

Consensus interferon

Pegylated IFN

Host factors TLR agonists therapeutic vaccines new interferons

2007
Pegylated Interferon-α (PEG-IFN)

- IFN-α conjugated to a
  - 40kD (PEG-α2a)
  - 12kD (PEG-α2b)
  - polyethylenglycol polymer

- longer halflife than standard IFN-alfa
- application only 1x / week
- higher AUC than 3x / week standard IFN-alfa
Type-I IFN induction and effector phase

**Induction Phase**
- Virus
- dsRNA
  - RIG-I / MDA-5
  - Cardif (IPS-1)
  - TBK-1 / IKKε
- IFN-β
  - TBK-1 / IKKε
  - IRF-3

**Effector Phase**
- dsRNA
  - TLR3
  - IFN-β
  - IFN-α/β
- IFNAR
- JAK-1 / TYK-2
- STAT-1
- IFN-α/β
- IRF-9
- ISIF-3
- ISRE
- ISG
- ADAR
- p56
- OAS
- PKR

Bartenschlager DGVS 2006