Autoimmune Hepatitis

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Acknowledgements

Richard Taubert

Elmar Jaeckel
Disclosure of Interest

Falk Pharma GmbH, Freiburg, Germany

Novartis, Basel, Switzerland
Diagnosis of Autoimmune Hepatitis

- Clinical Symptoms
- Biochemistry: ALT, AST, IgG
- Immunological Tests: Autoantibodies
- Genetics
- Histopathology
- Scoring Systems
- Differential Diagnosis
DIAGNOSIS OF AUTOIMMUNE HEPATITIS

- Female gender
- Extrahepatic autoimmune syndromes
- Hypergammaglobulinia (IgG)
- Autoantibodies: ANA, LKM-1, SMA, SLA/LP
- Genetics: HLA DR 3, DR 4, AIRE
- Histology
- Immunsuppressive Therapy
Diagnosis of AIH

Autoantibody Testing by Immunofluorescence

3 rodent tissue sections
- Kidney
- Stomach
- Liver

Hep2 cells

Neutrophils

ANA, SMA, AMA, LKM, LC1

ANA pattern

pANCA/pANNA

others: SLA, ASGPR

Manns et al. AASLD guidelines 2010, EASL CPG 2015
LIVER KIDNEY MIKROSOOMAL Antibodies: LKM
# Autoantibodies in Liver Diseases

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Target</th>
<th>Disease association</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>multiple nuclear antigens</td>
<td>AIH, SLE, MTCD etc.</td>
</tr>
<tr>
<td>AMA</td>
<td>2-oxo-acid-dehydrogenase complex</td>
<td>PBC</td>
</tr>
<tr>
<td>pANCA</td>
<td>h-Lamp-2, proteinase 3, Actin, troponin, tropomysin</td>
<td>AIH, PSC, PBC, AIH 1</td>
</tr>
<tr>
<td>SMA</td>
<td></td>
<td>AIH 2, HCV</td>
</tr>
<tr>
<td>LKM 1</td>
<td>CYP 2D6</td>
<td>Tienilic acid-induced hepatitis</td>
</tr>
<tr>
<td>LKM 2</td>
<td>CYP 2C9</td>
<td>AIH 2, hepatitis D</td>
</tr>
<tr>
<td>LKM 3</td>
<td>UGT1A</td>
<td>APS-1, hepatitis C</td>
</tr>
<tr>
<td>LKM</td>
<td>CYP 2A6</td>
<td>AIH 2</td>
</tr>
<tr>
<td>LC1</td>
<td>FTCD</td>
<td>AIH 3</td>
</tr>
<tr>
<td>SLA/LP</td>
<td>tRNP(Ser)Sec</td>
<td>Dihydralzine-induced hepatitis, APS-1</td>
</tr>
<tr>
<td>LM</td>
<td>CYP 1A2</td>
<td>Autoimmune liver disease, HCV</td>
</tr>
<tr>
<td>ASGP-R</td>
<td>Asialoglycoproteinrezeptor</td>
<td></td>
</tr>
</tbody>
</table>

Prof. Dr. med. M.P. Manns  
Department of Gastroenterology, Hepatology and Endocrinology  
14.01.2019
Autoantibodies in the Diagnosis of AIH

Liver disease of unknown origin

ANA, SMA, LMK-1, AMA

ANA+
SMA+
LKM1+
AMA+

AIH

Conventional tests negative

F-actin, SLA/LP, LC1, LKM3, PDH-E2, pANCA

AIH

F-actin +
SLA/LP +
LC1+ LKM3+
PDH-E2+

Negative

Cryptogenic chronic hepatitis

Atypical pANA+

F-actin +
SLA/LP +
LC1+ LKM3+
PDH-E2+

Negative

AIH

PBC

# Limitations of Autoantibodies in AIH

<table>
<thead>
<tr>
<th>Condition</th>
<th>ANA</th>
<th>SMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIH</td>
<td>60-85%</td>
<td>60-80%</td>
</tr>
<tr>
<td>NAFLD</td>
<td>12-40%</td>
<td>3-7%</td>
</tr>
<tr>
<td>NASH</td>
<td>20-40%</td>
<td>6-9%</td>
</tr>
<tr>
<td>HBV</td>
<td>15-30%</td>
<td>20-25%</td>
</tr>
<tr>
<td>HCV</td>
<td>9-40%</td>
<td>5-60%</td>
</tr>
<tr>
<td>PBC</td>
<td>20-50%</td>
<td>10%</td>
</tr>
<tr>
<td>PSC</td>
<td>7-70%</td>
<td>13-20%</td>
</tr>
</tbody>
</table>

**Meta-Analysis**

Zhang et al. *PloS One* 2014

**Hausdorff et al.**

*Clinica Clinica Acta* 2009

**Hannover retrospective Cohort**

n=237-270

Severity Of Autoimmune Hepatitis

Association of liver-related death or transplantation, n=240

No cirrhosis
n=122

Cirrhosis at diagnosis
N=89

Cirrhosis ? Time
N=5

Cirrhosis subsequently
N=24

Overall and LT-free Survival, n=354

Independent Risk Factor
Anti-SLA


# Classification Of Autoimmune Hepatitis Based On Autoantibodies

<table>
<thead>
<tr>
<th>Autoimmune hepatitis Type 1</th>
<th>Autoimmune hepatitis Type 2</th>
<th>Autoimmune hepatitis Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA, SMA</td>
<td>LKM-1, LKM-3, LC-1</td>
<td>SLA/LP</td>
</tr>
</tbody>
</table>

- **Autoimmune hepatitis Type 1**
  - 80% of cases
  - age: 16-30 years
  - slow onset

- **Autoimmune hepatitis Type 2**
  - 20% of cases
  - age: around 10
  - also fulminant cases

- **Autoimmune hepatitis Type 3**
  - similar to type 1
  - more relapse,
  - more difficult to treat

_AASLD Clinical Practice Guidelines: Hepatology 2010_
Diagnosis of Autoimmune Hepatitis: Histology

Interface hepatitis. Limiting plate of the portal tract is disrupted by a lymphoplasmacytic infiltrate.

Plasma cell infiltration.

Median centrilobular zone 3 necrosis. Centrilobular zone 3 necrosis associated with a mononuclear inflammatory infiltrate.
Autoimmune Hepatitis: Histopathology

- Interface hepatitis
- Plasmacelluar infiltrates
- Hepatocyte rosetting
- Emperipolesis
Autoimmune Hepatitis: Histopathology

- Alone not sufficient for AIH diagnosis

- But essential for diagnosis of AIH
  - Presence of characteristic features
  - Exclusion of other diseases

- Important for Grading and Staging

- Very important before stopping therapy

### AIH – Scores

**Alvarez et al. J Hepatol. 1999**

**Hennes et al. Hepatology 2008**

<table>
<thead>
<tr>
<th>Feature/parameter</th>
<th>Discriminator</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibodies (max 2 points)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA or SMA+</td>
<td>≥1:40</td>
<td>+1</td>
</tr>
<tr>
<td>ANA or SMA+</td>
<td>≥1:80</td>
<td>+2</td>
</tr>
<tr>
<td>or LKM+</td>
<td>≥1:40</td>
<td>+2</td>
</tr>
<tr>
<td>or SLA/LP+</td>
<td>Any titre</td>
<td>+2</td>
</tr>
<tr>
<td><strong>IgG or γ-globulins level</strong></td>
<td>≥ULN</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&gt;1.1x ULN</td>
<td>+2</td>
</tr>
<tr>
<td><strong>Liver histology</strong></td>
<td>Compatible with AIH</td>
<td>+1</td>
</tr>
<tr>
<td>(evidence of hepatitis is required)</td>
<td>Typical of AIH</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>Atypical</td>
<td>0</td>
</tr>
<tr>
<td><strong>Absence of viral hepatitis</strong></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>+2</td>
</tr>
</tbody>
</table>

Score ≥7 = Definite AIH  
Score ≥6 = Probable AIH

**Mieli-Vergani et al. JPGN 2017**

For paediatric AIH und AISC
- Lower auto-antibody titer
- Cholangiogram
- Family history for autoimmune diseases

Diagnosis of Autoimmune Hepatitis

• Clinical Symptoms
• Biochemistry: ALT, AST, IgG
• Immunological Tests: Autoantibodies
• Genetics
• Histopathology
• Scoring Systems
• Differential Diagnosis
Nivolumab is a monoclonal immunologically active antibody (IgG4), binding to the Immune-Checkpoint-Receptor (programmed death-1) PD-1 leading to Restoration of T-Cell-Activity.
## Treatment of AIH: Endpoints

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Criteria</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>Disappearance of clinical symptoms, <strong>Normalization</strong> of aminotransferases (ALT, AST), bilirubin und γ-globulins, Normal liver histology or inactive liver cirrhosis</td>
<td>Slow Reduction of steroids within 6 weeks, <strong>Control</strong> of serum AST, ALT, total-bilirubin, and γ-globulins in 3-week intervals during and 3 months after withdrawal, then every 6 months for 2 years, then every year</td>
</tr>
</tbody>
</table>

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Application of the 2010 AASLD criteria of remission to a cohort of Italian patients with autoimmune hepatitis

- **AIH (n=163)**
  - **TREATMENT**
    - Remission n=119 (73%) [AASLD 2002]
    - Remission n=42 (26%) [AASLD 2010]

**Remission AIH (>60 months)**
- methylprednisolone 2-4 mg/daily or every other day
- N=89
  - 23 (25.8%) Normal ALT [AASLD 2010]
  - 65 (73%) ALT<2xULN [AASLD 2002]
  - 1 (4%) Histological worsening of the disease
  - 36 (54.5%)
# AASLD CPG: First Line Treatment of AIH (adults)

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prednisone</td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td>(mg/ day)</td>
<td>USA (mg/ day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EU (mg/ kg/ day)</td>
</tr>
<tr>
<td>Week 1</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>1 - 2</td>
</tr>
<tr>
<td>Week 2</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1 - 2</td>
</tr>
<tr>
<td>Week 3</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Week 4</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1 – 2</td>
</tr>
<tr>
<td>Maintenance-Therapy</td>
<td>20 and less</td>
<td>10</td>
</tr>
<tr>
<td>Reasons for Choice of Therapy</td>
<td>Cytopenia, Thiopurinmethyl-transferase-Deficiency, Pregnancy, Tumors, Therapy ≤6 Mo</td>
<td>Postmenopausal, Osteoporosis, uncontrolled Diabetes, Hypertension, Obesity, Acne, Emotional Instability</td>
</tr>
</tbody>
</table>

Management of AIH in adults


Mieli-Vergani, G. et al. (2018) Autoimmune hepatitis

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14.01.2019
Management of AIH in adults

Differences of high (≥0.5mg/kg) and low (<0.5mg/kg) dose prednisolone regimen during first line therapy

451 AIH patients from 9 centers in 5 European countries treated between 1978 and 2017

Biochemical remission after 6 months:
- ≥0.5mg/kg/day (n=281): 70.5%
- <0.5mg/kg/day (n=170): 64.7%
  
Cumulative steroid dose over 6 months (mg):
- ≥0.5mg/kg/day: 3780 mg
- <0.5mg/kg/day: 2573 mg

Steroid specific side effects:
- ≥0.5mg/kg/day: 21.3%
- <0.5mg/kg/day: 18.8%

Second Line Therapy for AIH: Alternative Drugs

Safety (Intolerance) versus Efficacy
## Frequency and Nature of Side Effects (Adults)

<table>
<thead>
<tr>
<th>Prednisone-Related Side Effects</th>
<th>Frequency</th>
<th>Azathioprine-Related Side Effects</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td></td>
<td><strong>Type</strong></td>
<td></td>
</tr>
<tr>
<td>Cosmetic (usually mild)</td>
<td></td>
<td>Hematologic (mild)</td>
<td></td>
</tr>
<tr>
<td>Facial rounding, Weight gain, Dorsal hump striae, Hirsutism, Alopecia</td>
<td>80% (after 2 years)</td>
<td>Cytopenia</td>
<td>46% (especially with cirrhosis)</td>
</tr>
<tr>
<td>Somatic (usually mild)</td>
<td></td>
<td>Hematologic (severe)</td>
<td></td>
</tr>
<tr>
<td>Emotional Instability, Glucose intolerance, Cataract</td>
<td>13% (Treatment ending)</td>
<td>Leukopenia</td>
<td></td>
</tr>
<tr>
<td>Hematologic (mild)</td>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Somatic (severe)</td>
<td></td>
<td>Somatic (mild)</td>
<td></td>
</tr>
<tr>
<td>Osteopenia, Vertebral compression, Diabetes (brittle), Psychosis, Hypertension (labile)</td>
<td></td>
<td>Nausea, Emesis, Rash, Fever, Arthralgias</td>
<td>5%</td>
</tr>
<tr>
<td>Somatic (severe)</td>
<td></td>
<td>Neoplastic</td>
<td></td>
</tr>
<tr>
<td>Inflammatory/Neoplastic</td>
<td></td>
<td>Hematologic /enteric</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis, Opportunistic infection, Malignancy</td>
<td>Rare</td>
<td>Bone marrow failure, villous atrophy, Malabsorption</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
<td>Teratogenic</td>
<td>Rare (theoretical)</td>
</tr>
</tbody>
</table>

Decrease of Steroid Specific Side Effects in Patients Switched from Prednisone to Budesonide (n=87)


Month 6

Month 12

P<0.0001*

*McNemar’s test for paired proportions
Role of Budesonide

- Instead of Prednisolone to reduce side effects in combination with Azathioprine
  - Induction of remission in risk patients for steroid specific side effects (SSSE)
  - Long-term maintenance of remission

- Approved for AIH in 23 European and 13 Non-European countries
Budesonide Versus Prednisone: Limitations

EDITORIAL:

The right drug at the right time for the right patient

Manns, Jaeckel, Taubert, Clin Gastroenterol Hepatol, 2018
### Frequency and Nature of Side Effects (Adults)

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<tr>
<td><strong>Somatic (severe)</strong></td>
<td></td>
<td><strong>Hematologic (severe)</strong></td>
<td></td>
</tr>
<tr>
<td>Osteopenia, Vertebral compression, Diabetes (brittle), Psychosis, Hypertension (labile)</td>
<td></td>
<td>Leukopenia</td>
<td>6% (Treatment ending)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory/Neoplastic</strong></td>
<td>Rare</td>
<td><strong>Somatic (mild)</strong></td>
<td>5%</td>
</tr>
<tr>
<td>Pancreatitis, Opportunistic infection, Malignancy</td>
<td></td>
<td>Nausea, Emesis, Rash, Fever, Arthralgias</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neoplastic</strong></td>
<td>3% (after 10 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hämatologic /enteric</strong></td>
<td>Rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow failure, villous atrophy, Malabsorption</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Teratogenic</strong></td>
<td>Rare (theoretical)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Routine assessment of thiopurine methyltransferase (IPMT)?**

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Mycophenolate Mofetil (MMF) as Second Line Therapy – Retrospective Analysis

- MMF in n = 36 patients
  - n = 27 due to AZA intolerance
  - n = 9 due to AZA insufficiency

- Remission: < 2x ULN
- Total Remission to MMF: 14/36 (38 %)
- Remission in AZA intolerant pts: 12/28 (~ 43 %)
- Remission in AZA failure pts: 02/08 (~ 25 %)

- MMF should be considered in AZA intolerant patients

Second Line Therapy for AIH: Alternative Drugs

Safety (Intolerance) versus Efficacy
# Second Line Therapy for Treatment Failures: Alternative Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine A</td>
<td>3-5 mg/kg kg/qd</td>
<td>hypertension, renal insufficiency</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>3 mg bid</td>
<td>hypertension</td>
</tr>
<tr>
<td>Mycophenolate Mofetil</td>
<td>750-1000 mg bid</td>
<td>Diarrhea, leucopenia</td>
</tr>
<tr>
<td>6-thioguanine</td>
<td>20 mg/day</td>
<td></td>
</tr>
<tr>
<td>6-mercaptopurine</td>
<td>1.5 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10 mg per week</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1-1.5 mg/kg/day</td>
<td>Cystitis, leucopenia</td>
</tr>
<tr>
<td>Everolimus</td>
<td>0.75-1.5mg bid</td>
<td>Proteinuria, lipid disturbance, ulcera</td>
</tr>
<tr>
<td></td>
<td>(3-6ng/ml)</td>
<td></td>
</tr>
</tbody>
</table>

**NONE OF THESE SECOND LINE THERAPIES IS APPROVED!**
Management of failures to standard of care

- Biologicals
  - Anti TNF
  - Anti CD 20 (Rituximab)
  - Anti B cell and anti BAFF-R (VAY736)
Treatment of refractory AIH with anti-TNF

Weiler-Norman et al. J Hepatol 2013
Anti-TNF alpha may cause AIH

• Induction of AIH following TNF alpha antagonists:
  
  - Harada K et al. Clin Rheumatol 2008 AIH Exacerbation following Etanercept in patients with rheumatoid arthritis
  
  
  - Cravo M. BioDrugs 2010 AIH induced by Infliximab in a patient with Crohn's disease, no relapse after switch to adalimumab
Rituximab Treatment of AIH

Chimeric monoclonal antibody against B cell marker CD20
Rituximab response: case reports

- Burak 2013: 1
- Burak 2013: 2
- Burak 2013: 3
- Burak 2013: 4
- Burak 2013: 5
- Burak 2013: 6
- Santos 2006
- Barth 2010
- D’Agostino 2013: 1 (BL=16 x ULN)
- D’Agostino 2013: 2 (BL = 30 x ULN)

Approx 12 w
Rituximab treatment experience in patients with complicated type 1 autoimmune hepatitis in Europe and North America

- 22 patients, retrospective analysis, UK, Canada Germany
- Before and 24 months after RTX
- Reduction of Prednisolone and freedom of flares
- Improvement of ALT, AST and sustained for 24 months, (p < 0.0010)

- ALT 167 IU/L to 32 IU/L  (p< 0.001)
- AST 127 IU/L to 29 IU/L
- IgG 18.9 g/l to 13.2 g/L  (p< 0.001)

Than et al, EASL 2018, J Hepatol, 68, S217-8, 2018
Rituximab – Complications and Adverse Events

• Usually mild, infrequent:
  – Infusion reactions, bacterial infections, neutropenia, anemia, rash, fever, diarrhea, reactivation of viral infections

• But include:
  – Late onset neutropenia, rheumatic disease, HBV reactivation, activation of a latent polyoma virus (JC virus) with multifocal leucoencephalopathy
Molecular pathogenesis of autoimmune hepatitis

Manns et al., Journal of Hepatology, 2015

VAY736 = lanalumab
AIH: Future Therapies

• Can we increase therapeutic response by strengthening immunoregulation?

• Anti CD 3

• Low dose IL-2

• Adoptive transfer of Tregs?
Molecular pathogenesis of autoimmune hepatitis

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Department of Gastroenterology, Hepatology and Endocrinology
14.01.2019

Manns et al., Journal of Hepatology, 2015
Regulatory T cells (Treg): Numbers and function

No numerical Dysfunction of intrahepatic Treg

Selective Treg depletion under standard therapy

Higher intrahepatic Treg in remission

modified from Taubert et al. J Hepatol. 2014;61(5):1106-14

Similar findings by multiple centers

Oo et al. JI 2010; Peiseler et al. J Hepatol 2012
Renand et al. Hepatol. Commun. 2018

modified from Taubert et al. J Hepatol. 2014;61(5):1106-14
Regulatory T cells (Treg): Numbers and function

Freshly isolated liver infiltrating CD4+CD25^{high}CD127^{low} Treg

Liver supernatant

Serum IL-2


modified from: Jeffery et al. HEPATOLOGY COMMUNICATIONS, Vol. 2, No. 4, 2018
Low dose IL-2 in refractory AIH

modified from Lim et al., Hepatology, 2018

female 20 yrs. with cirrhosis (pediatric AIH-1)

female 56 yrs. with bridging fibrosis (adult AIH-3)

(1 Mio. Units s.c. 5x/month over 6 months)
Relapse occurs rapidly after treatment withdrawal
- Incidence of relapse or loss of remission
  - 59% after 1 year
  - 73% after 2 years
  - 81% after 3 years

In patients with combination therapy at start of withdrawal
- Risk of relapse was higher
- Time to relapse was shorter

Probability of remission after drug withdrawal*

*All patients had been in remission for at least 2 years prior to drug withdrawal
Van Gerven et al. J Hepatol 2013;58:141–7
EASL CPG AIH. J Hepatol 2015;63:971–1004
Chloroquine for Maintenance of Remission in AIH (single center RCT in Brazil)

61 AIH pts. with histologic Remission (HAI<4) among which:
- 30 pts. received Placebo for 36 months
- 31 pts. received CQ 250mg/d for 36 months

Relapse free survival:
- CQ group: 19.9% relapse
- Placebo group: 59.3% relapse
- p = .039

Other adverse events:
- Any AE: CQ (17/31, 54.8%) vs. Placebo (5/30, 16.7%)
- Discontinuation due to AE: CQ (6/31, 19.3%) vs. Placebo (3/30, 10%)
- Classification according to Naranjo algorithm:
  - Definite (0/31 vs. 0/30)
  - Probable (4) vs. Probable (0)
  - Possible (12) vs. Possible (3)
  - Doubtful (1) vs. Doubtful (2)

Grade 3/4:
- CQ: 0
- Placebo: 0

Terrabuio et al., Hepatol Commun, 2019
Thank you for your attention

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