Autoimmune Hepatitis – Challenges in Diagnosis and Treatment

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HASLD Meeting
Ho Chi Minh City, 16 December 2018
Acknowledgements

Elmar Jaeckel

Richard Taubert
Disclosure of Interest

Falk Pharma GmbH, Freiburg, Germany

Intercept,

Gilead Sciences, Foster City, USA

Novartis, Basel, Switzerland
Autoimmune Liver Diseases

- Autoimmune hepatitis (AIH)
- Primary Biliary Cholangitis (Cirrhosis) (PBC)
- Primary Sclerosing Cholangitis (PSC)
AASLD PRACTICE GUIDELINES

Diagnosis and Management of Autoimmune Hepatitis

Michael P. Manns,1 Albert J. Czaja,2 James D. Gorham,3 Edward L. Krawitt,4 Giorgina Mieli-Vergani,5 Diego Vergani,6 and John M. Vierling7

AASLD Practice Guidelines: Hepatology 2010

October 2015

Clinical Practice Guidelines

EASL Clinical Practice Guidelines: Autoimmune hepatitis∗

European Association for the Study of the Liver∗

www.easl.eu: Journal of Hepatology 2015
Diagnosis of Autoimmune Hepatitis

- Clinical Symptoms
- Biochemistry
- Immunological Tests: Autoantibodies
- Genetics
- Histopathology
- Scoring Systems
- Differential Diagnosis
Challenges in the diagnosis of AIH

• Diagnostic criteria

• Autoantibodies

• Histology

• Differential Diagnosis: DILI, Viral Hepatitis, APECED, etc
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
# Disease Associations of Autoimmune Liver Diseases

<table>
<thead>
<tr>
<th>Autoimmune hepatitis: AIH</th>
<th>Primary biliary cholangitis: PBC</th>
<th>Primary sclerosing cholangitis: PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune thyroiditis</td>
<td>Keratoconjunctivitis sicca</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Grave’s disease</td>
<td>Xerostomia</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Sjögren’s syndrome</td>
<td>Histiocytosis X</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Scleroderma/CREST syndrome</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenia</td>
<td>Rheumatoid arthritis</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Autoimmune thyroiditis</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Celiac disease</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Mixed connective tissue</td>
<td>Retroperitoneal fibrosis</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>Renal tubular acidosis</td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis of Autoimmune Hepatitis

• Clinical Symptoms
• **Biochemistry: ALT, AST, IgG**
• Immunological Tests: Autoantibodies
• Genetics
• Histopathology
• Scoring Systems
• Differential Diagnosis
## 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, Normalization of aminotransferases (ALT, AST), bilirubin und γ-globulins Normal liver histology or inactive liver cirrhosis</td>
<td>Slow Reduction of steroids within 6 weeks Control 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>

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

**Remission**

- **AIH (n=163)**

  **TREATMENT**

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

**Remission AIH (>60 months)**

- Methyiprednisolone 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%)
Challenges in the diagnosis of AIH

- Diagnostic criteria
- Scoring systems
- Role of Autoantibodies
- Histology
- Differential Diagnosis: DILI, Viral Hepatitis, APECED, etc
AIH – Scores

Alvarez et al. J Hepatol. 1999

<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></td>
<td></td>
</tr>
<tr>
<td>&gt;ULN</td>
<td></td>
<td>+1</td>
</tr>
<tr>
<td>&gt;1.1x ULN</td>
<td></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
Challenges in the diagnosis of AIH

- Diagnostic criteria

- Scoring systems

- Role of Autoantibodies

- Histology

- Differential Diagnosis: DILI, Viral Hepatitis, APECED, etc
Diagnosis of AIH

Autoantibody Testing by Immunofluorescence

3 rodent tissue sections

Kidney

Stomach

Liver

Hep2 cells

ANA, SMA, AMA, LKM, LC1

ANA pattern

Neutrophils

pANCA/pANNA

Prof. Dr. med. M.P. Manns
Department of Gastroenterology, Hepatology and Endocrinology
11.04.2018

Manns et al. AASLD guidelines 2010, EASL CPG 2015
LIVER KIDNEY MIKROSONMAL Antibodies: LKM
Variability of antinuclear Antibodies

Strassburg, Manns J Hepatol. 1999

homogenous Immunfluorescence

Nucleus: Immunfluorescence

“nuclear dots” Immunfluorescence
Molecular Pathogenesis Of Autoimmune Hepatitis
Autoantibodies in Liver Diseases

• Useless epiphenomena?
• Diagnostic reagents
• Probes to identify aetiological agents
• Probes to identify significant molecules for cell biology
  - Cytochrome P450s
  - Acyltransferases
  - UGT-glucuronosyltranferases
  - RNA-Binding Proteins
  - Membrane Receptors
  - Cytosolic enzymes
  - etc.
# Autoantibodies in Liver Diseases

<table>
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<tr>
<th>Autoantibodies</th>
<th>Target</th>
<th>Disease association</th>
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<tbody>
<tr>
<td>ANA</td>
<td>multiple nuclear antigens</td>
<td>AIH, SLE, MTCD etc.</td>
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<td>AMA</td>
<td>2-oxo-acid-dehydrogenase complex</td>
<td>PBC</td>
</tr>
<tr>
<td>pANCA</td>
<td>h-Lamp-2, proteinase 3,</td>
<td>AIH, PSC, PBC</td>
</tr>
<tr>
<td>SMA</td>
<td>Actin, troponin, tropomyosin</td>
<td>AIH 1</td>
</tr>
<tr>
<td>LKM 1</td>
<td>CYP 2D6</td>
<td>AIH 2, HCV</td>
</tr>
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<td>LKM 2</td>
<td>CYP 2C9</td>
<td>Tienilic acid-induced hepatitis</td>
</tr>
<tr>
<td>LKM 3</td>
<td>UGT1A</td>
<td>AIH 2, hepatitis D</td>
</tr>
<tr>
<td>LKM</td>
<td>CYP 2A6</td>
<td>APS-1, hepatitis C</td>
</tr>
<tr>
<td>LC1</td>
<td>FTCD</td>
<td>AIH 2</td>
</tr>
<tr>
<td>SLA/LP</td>
<td>tRNP(Ser)Sec</td>
<td>AIH 3</td>
</tr>
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<td>LM</td>
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Prof. Dr. med. M.P. Manns  
Department of Gastroenterology, Hepatology and Endocrinology  
11.04.2018
Threedimensional Structure of CYP2D6: LKM-1

- Novel Epitope
  - Sugimura et al. Autoimmunity December 2002

- Major Linear Epitope
  - Manns et al, JCI, 1989
  - HSV 175 !!!!

- Minor Epitope
  - 352-379
  - 321-351
  - 257-269
  - 410-429
  - 373-389
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Department of Gastroenterology, Hepatology and Endocrinology  
11.04.2018

Hannover Medical School
CYPs and UGTs: Targets for Immune Reactions

Manns and Obermayer, Hepatology, 2002
Diagnosis of AIH

Autoantibody Testing by Immunofluorescence

3 rodent tissue sections

Kidney

Stomach

Liver

Hep2 cells

ANA, SMA, AMA, LKM, LC1

ANA pattern

pANCA/pANNA

Neutrophils

others: SLA, ASGPR

Prof. Dr. med. M.P. Manns
Department of Gastroenterology, Hepatology and Endocrinology
11.04.2018

Manns et al. AASLD guidelines 2010, EASL CPG 2015
The SLA Story

**SLA**

Manns et al. Lancet 1987  
Wächter et al. J Hepatol 1990  
Wesierska-Gadek et al. Gastro 1996  
Ma et al. Hepatol 2002

**LP**

Berg et al. DGIM 1981  
Stechemesser et al. Hepatology 1993

Anti **SLA/LP** antibodies recognize a serine tRNA associated 48-50 kD protein

Molecular Cloning of SLA/LP antigen

Wies et al. Lancet 2000  
Volkmann et al. J Hepatol 2000  
Kernebeck 2001 Hepatol 2001

Antibodies against Serine tRNA-associated protein in a subgroup of severe AIH

Gelpi et al. PNAS 1992
## Classification of Autoimmune Hepatitis Based on Autoantibodies

<table>
<thead>
<tr>
<th>Autoimmune Hepatitis Type 1</th>
<th>ANA, SMA</th>
<th>80% of cases, age: 16-30 years, slow onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Hepatitis Type 2</td>
<td>LKM-1, LKM-3, LC-1</td>
<td>20% of cases, age: around 10, also fulminant cases</td>
</tr>
<tr>
<td>Autoimmune Hepatitis Type 3</td>
<td>SLA/LP</td>
<td>similar to type 1, more relapse, more difficult to treat</td>
</tr>
</tbody>
</table>
Severity Of Autoimmune Hepatitis

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

Overall and LT-free Survival, n=354

No cirrhosis
n=122

Cirrhosis at diagnosis
N=89

Cirrhosis ? Time
N=5

Cirrhosis subsequently
N=24

x²=24, P<0.001

P=0.000; log rank

Independent Risk Factor
Anti-SLA


Survival

Overall survival by Anti-SLA/LP

Overall survival by histology

Overall and LT-free survival by Anti-SLA/LP

Overall and LT-free survival by histology

p = 0.082; log rank

p = 0.002; log rank

p = 0.118; log rank

p = 0.000; log rank
Autoantibodies in the Diagnosis of AIH

Liver disease of unknown origin

ANA. SMA, LMK-1, AMA

ANA+ SMA+ LKM1+ AMA+

Conventional tests negative

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

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

Atypical pANA+

AIH

PSC

Cryptogenic chronic hepatitis

# Limitations of Autoantibodies in AIH

<table>
<thead>
<tr>
<th></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**
- **Hausdorf et al. Clinica Clinica Acta 2009**
- **Hannover retrospective Cohort n=237-270**

Challenges in the diagnosis of AIH

• Diagnostic criteria

• Scoring systems

• Role of Autoantibodies

• Histology

• Differential Diagnosis: DILI, Viral Hepatitis, APECED, etc
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
- Plasmacellular infiltrates
- Hepatocyte rosetting
- Emperipolesis
Typical histopathology of AIH

A. Typical histopathology of AIH with portal/peripoortal predominance of necroinflammatory lesions and broad interface hepatitis

B. Emperipolesis with a lymphocyte in the cytoplasm of a damaged hepatocyte

C. Typical rosetting of hepatocytes in the area of interface hepatitis

Gurung et al. Hum Pathol. 2018

Typical AIH:
Plasma cells + Kupffer cell hyaline Globules

Compatible AIH:
Plasma cells but no KcHG

not significantly associated with AIH, when matched for severity of inflammation (HCV control)

Histopathology pictures were provided by Hans Peter Dienes, University of Vienna, Austria
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

Challenges in the diagnosis of AIH

• Diagnostic criteria

• Autoantibodies

• Histology

• Differential Diagnosis: Viral Hepatitis, DILI, APECED, ....
Hepatitis E – breaker of hepatic tolerance?

- Anti-HEV T cell reactivity in all anti-HEV+ AIH patients
- HEV replication only in 1/208 AIH patients with clearance under reduced immunosuppression

Wantai assay (p=0.05)
Pathophysiology – Hepatitis E and other viruses


Taubert et al. under review

Taubert et al. under review
Drug Induced Liver Injury (DILI): 2 Modes of Action

Hepatotoxins

Toxic Liver Injury
• Predictable
• Dose dependent
• Reproducible in animals

Idiosyncratic Liver Injury
• Not predictable
• Dose independent
• Increased risk at re-expose

„Hepatoallergens“

Direct Toxicity through substance

Indirect Toxicity through intermediates

Augmentan

Amanita

Paracetamol

Isoniazid

Phenprocoumon (Marcumar)
### Pathophysiology – Drug induced AIH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minocycline</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td></td>
</tr>
<tr>
<td>Hydralazine (dihydralazine)</td>
<td>induction of anti-cytochrome P4501A2 autoantibodies</td>
</tr>
<tr>
<td>Methylldopa</td>
<td></td>
</tr>
<tr>
<td>α- and β-interferons</td>
<td></td>
</tr>
<tr>
<td>Infliximab, adalimumab, etanercept</td>
<td>anti-TNFα blockade</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA4 blockade and regulatory T cell depletion</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1 blockade</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td></td>
</tr>
<tr>
<td>Khat and black cohosh</td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td></td>
</tr>
<tr>
<td>Tienelic acid</td>
<td>Cytochrome P450 2C9</td>
</tr>
</tbody>
</table>

Mechanism of immune mediated indirect hepatotoxicity

Activated Enzyme
- Dihydralazin CYP1A2
- Ticrynafen CYP2C9
- Halothane CYP2E1

Other cellular proteins
- Halothane
- Ethanol

"modified self " Epitope

Immunoreaction

modifiziert according to P. Beaune
Drug-Enzyme-Adduct Formation
Immune mediated hepatotoxicity / Apoptosis

Drug-Enzyme Adduct Formation
Oxidative Stress
→ Hepatocellular Injury

Neo-Antigens → Immune response → Cytokines
→ Apoptosis

Autoantibodies

Target Antigens for Autoantibodies in DILI

- Chronic Hepatitis C
- Autoimmune Hepatitis
- Chronic Hepatitis D
- Addison Disease
- Adrenal Failure in APS1
- Gonadal Failure in APS1
- CYP2A6, CYP1A2, CYP2D6, CYP21
- CYP11beta, CYP17
- UGT1, CYP2E1, rCYP3A1, rCYP2C11, CYP2C9

- Hepatitis in APS1
- Dihydralazine Hepatitis
- Alcoholic Cirrhosis
- Halothane Hepatitis
- Anticonvulsant Hepatitis
- Tienilic Acid Hepatitis

Obermayer–Straub, Manns, Hepatology, 2000
immune check points – therapeutic Targets

- Nivolumab
- Pembrolizumab
- Pidilizumab
- Ipilimumab
- Tremelimumab

Nivolumab is a monoclonal immunologically active antibody (IgG4), binding to the Immune-Checkpoint-Receptor (programmed death-1) PD-1
Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

A thumbnail of the paper is provided.

Safety

CheckMate 040 Dose Escalation & Expansion

<table>
<thead>
<tr>
<th>Uninfected</th>
<th>HCV Infected (n = 61)</th>
<th>HBV Infected (n = 66)</th>
<th>All Patients (n = 262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Grade 3/4</td>
<td>Any Grade 3/4</td>
<td>Any Grade 3/4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (8) 4 (3)</td>
<td>6 (10) 5 (8)</td>
<td>2 (3) 2 (3)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>91 (67) 54 (18)</td>
<td>45 (74) 21 (34)</td>
<td>61 (76) 51 (19)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (7) 7 (11)</td>
<td>7 (11) 0</td>
<td>16 (6) 0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (5) 0</td>
<td>3 (8) 0</td>
<td>13 (5) 0</td>
</tr>
<tr>
<td>Laboratory treatment-related AE</td>
<td>13 (10) 10 (16)</td>
<td>10 (16) 10 (16)</td>
<td>23 (9) 14 (5)</td>
</tr>
<tr>
<td>AST increase</td>
<td>11 (8) 3 (2)</td>
<td>9 (15) 6 (10)</td>
<td>22 (6) 9 (3)</td>
</tr>
<tr>
<td>ALT increase</td>
<td>10 (7) 4 (3)</td>
<td>3 (5) 1 (2)</td>
<td>15 (6) 8 (2)</td>
</tr>
<tr>
<td>Lipase increase</td>
<td>10 (7) 7 (5)</td>
<td>5 (8) 2 (3)</td>
<td>17 (6) 13 (5)</td>
</tr>
</tbody>
</table>

Treatment-related AEs led to discontinuation in 4% of patients.

No treatment-related deaths occurred in either the escalation or expansion cohorts.
Suggested algorithm for AIH vs DILI

Probable or possible AIH vs DILI

0.5–1 mg/kg prednisolone

Response

Taper steroids until withdrawal

Relapse

Definite AIH

Treatment of AIH

Non-response

Consider alternative diagnoses

No relapse

DILI*

Avoid this drug in future

*Long-term follow-up is advised in order not to miss a late relapse of AIH (e.g. 6 monthly for 3 years)

EASL CPG AIH. J Hepatol 2015;63:971–1004
Challenges in the diagnosis of AIH

- Diagnostic criteria
- Autoantibodies
- Histology
- Differential Diagnosis: Viral Hepatitis, DILI, APECED, ....
Autoimmune Polyendocrinopathy Syndrome Type 1 (APS-1, APECED)

Endocrine Components
- Testicular Failure
- Ovarian Failure
- Hypothyroidism
- Parietal-Cell Atrophy
- IDDM
- Adrenal Failure
- Hypoparathyroidism

Nonendocrine Components
- Candidiasis
- Alopecia
- Vitiligo
- Keratopathy
- Hepatitis
- Malabsorption
- Enamel Hypoplasia
- Tympanic Membrane Calcification
- Nail dystrophy

% Patients

Ahonen et al. New England of Medicine 1999
Autoimmune Regulator AIRE

- Identified by positional cloning in 1997
- Chromosome 21q22.3, 13kb in length, 14 exons
- Expression mainly in thymus and to lesser extent in other lymphoid organs
- not detectable in target cells
- Transcriptional transactivator
- More than 50 mutations identified in APS-1 patients

Nagami et al., Nature Genetics 1997
Finnish-German Consortium, Nature Genetics 1997

Kumar et al. Journal of Biological Chemistry 2001
Heino et al., European Journal of Immunology 2000
### Overlap in Targets of Autoimmunity: Idiopathic Autoimmune Diseases versus APECED/APS-1

<table>
<thead>
<tr>
<th></th>
<th>Idiopathic</th>
<th>APECED/APS-1 related</th>
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<tbody>
<tr>
<td>Adrenal Insufficiency</td>
<td>CYP 21</td>
<td>CYP 21 CYP17 CYP11A</td>
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<tr>
<td>Hypoparathyroidism</td>
<td>Ca(^{2+})-sensing receptor</td>
<td>Ca(^{2+})-sensing receptor</td>
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<tr>
<td>Diabetes</td>
<td>GAD 65</td>
<td>GAD 65</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>CYP 2D6, UGT1A, LC-1</td>
<td>CYP1A2, CYP1A6, AADC</td>
</tr>
</tbody>
</table>

Obermayer et al, Gastroenterology, 2002