Αυτοάνοσες / χολοστατικές παθήσεις του ήπατος: τι αλλάζει στην φαρμακευτική αντιμετώπισή τους

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Γενικό Ογκολογικό Νοσοκομείο Κηφισιάς «ΟΙ ΑΓΙΟΙ ΑΝΑΡΓΥΡΟΙ»

13η ΠΑΝΕΛΛΗΝΙΑ ΕΚΠΑΙΔΕΥΤΙΚΗ ΣΥΝΑΝΤΗΣΗ ΕΛΙΓΑΣΤ ΕΞΕΛΙΞΕΙΣ ΣΤΗ ΓΑΣΤΡΕΝΤΕΡΟΛΟΓΙΑ ΚΑΙ ΗΠΑΤΟΛΟΓΙΑ ΑΘΗΝΑ, 23-25 ΦΕΒΡΟΥΑΡΙΟΥ 2018
Conflict of Interest

None
Treatment of AIH should be aimed to obtain **complete biochemical and histological resolution of the disease** in order to prevent further progression of liver disease (II-2).

- **Biochemical remission** is defined as normalisation of IgG and transaminases.
- **Histological remission** is defined as normal histology or minimal hepatitis (HAI <4 or equivalent) (II-2)

**EASL CPG AIH, J Hepatol 2015;63:971-1004**
### AASLD CPG: First Line Treatment of AIH (adults)

#### Diagnosis and management of autoimmune hepatitis

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prednisone</td>
<td>Prednisone Azathioprine</td>
</tr>
<tr>
<td>(mg/day)</td>
<td>(mg/day)</td>
<td>USA (mg/day)</td>
</tr>
<tr>
<td>Week 1</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>Week 2</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Week 3</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Week 4</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Maintenance-therapy</td>
<td>20 and less</td>
<td>10</td>
</tr>
</tbody>
</table>

**Reasons for Choice of Therapy**
- Cytopenia
- Thiopurinmethyltransferase-Deficiency
- Pregnancy
- Tumors
- Therapy < 6 Mo
- Postmenopausal
- Osteoporosis
- Uncontrolled Diabetes, Hypertension, Obesity
- Acne
- Emotional Instability

*high efficacy with minimal side effects*

Triggering factors of acute liver failure as a first manifestation of AIH – investigations on 565 patients

- 565 patients with histologically proven AIH
- 52 / 565 (9.2%) patients fulfilled the criteria for ALF*
- Able to identify triggering factors in 26/52 (50%)
- 6/52 (11.5%) did not survive ALF
- 3/52 (5.7%) underwent LT

**Mortality risk factors**: advanced age, ↑ MELD-score, ↑ creatinine

*INR > 1.5 plus overt encephalopathy

Table 1: Patients’ demographics and laboratory data:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.0 ± 14.9</td>
</tr>
<tr>
<td>Gender</td>
<td>44 f / 8 m</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>1’391 ± 1’117</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>14.3 ± 7.7</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.76 ± 0.34</td>
</tr>
<tr>
<td>INR</td>
<td>1.78 ± 0.61</td>
</tr>
<tr>
<td>MELD-Score</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>Immunoglobulin G (g/l)</td>
<td>17.2 ± 7.2</td>
</tr>
<tr>
<td>γ-Globulin Fraction (%)</td>
<td>24.5 ± 8.9</td>
</tr>
</tbody>
</table>

Buechter et al, AASLD 2017
Flare of AIH as a cause of ACLF and its response to steroid therapy

- 285 ACLF patients enrolled in the AARC database – **2.9% AIH**
- 8 (9.7%) had DILI & 6 (7.3%) had viral infection as possible precipitating factor for AIH

**ACLF per APASL definition:**
“The ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dl) and coagulopathy (INR ≥1.5) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis

**Serology**

- ANA (1:80) 43.9%
- SMA 19.5%
- LKM-1 3.7%
- Seronegative 49%
- Seropositive; 51%

*Anand et al, AASLD 2017 (on behalf of APASL ACLF working party)*
Flare of AIH as a cause of ACLF and its response to steroid therapy

• Group A receive corticosteroids (n=28), group B did not (n=54); similar baseline characteristics

• Median length of ICU stay in group A significantly lower (1.5d [0-4] vs. 4d [0-13]); p<0.001

• On fup, 6 (21.4%) patients in group A had new onset sepsis vs. 7 (12.9%) in group B; p=0.32

• On multivariate analysis, only MELD score (<27) favorably predicted steroid response with AUROC 0.86

CONCLUSION
Early stratification (MELD<27) to steroid therapy or LT (MELD>27) would reduce ICU stay and help improve outcomes

Anand et al, AASLD 2017 (on behalf of APASL ACLF working party)
Acute severe AIH: Prognostic factors of steroid treatment response

Which are predictive factors for corticosteroid response defined by the LT-free survival?

<table>
<thead>
<tr>
<th></th>
<th>Responders* N= 77</th>
<th>Non Responders* N= 36</th>
<th>p</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52 [39-63]</td>
<td>54 [41-61]</td>
<td>0.9803</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, female</td>
<td>58 (75)</td>
<td>24 (67)</td>
<td>0.3365</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HE</td>
<td>1 (1)</td>
<td>5 (14)</td>
<td>0.0185</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>784 [407-1120]</td>
<td>699 [408-1124]</td>
<td>0.9067</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, µmol/L</td>
<td>272 [207-386]</td>
<td>346 [265-414]</td>
<td>0.0803</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, µmol/L</td>
<td>59 [52-72]</td>
<td>63 [50-71]</td>
<td>0.9374</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, G/L</td>
<td>202 [145-275]</td>
<td>130 [81-196]</td>
<td>0.0007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>13 (19)</td>
<td>13 (36)</td>
<td>0.0468</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission corticosteroids, days</td>
<td>7 [3-10]</td>
<td>4 [2-9]</td>
<td>0.4058</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis stage 0-1/ 2-3/ 4</td>
<td>29(43)/27(40)/12(18)</td>
<td>14(56)/3(12)/8(32)</td>
<td>0.0333</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 2 patients were excluded, 1 dead and 1 LT before day 3 of corticosteroid therapy

The continuous variables are expressed using median [range IQR 1st and 3rd]. The qualitative variables are expressed using number (%).

De Martin et al, AASLD 2017
Acute severe AIH: Prognostic factors of steroid treatment response

*Which are predictive factors for corticosteroid response defined by the LT-free survival?*

**CONCLUSION:** Corticosteroid response was 65% and independent predictors were INR, the improvement of total bilirubin at day 3 and at day 7 of therapy.

<table>
<thead>
<tr>
<th></th>
<th>Responders N=77</th>
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<th>p</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta ALT d3-d0</td>
<td>-132 [-391/-45]</td>
<td>-89 [-317/-13]</td>
<td>0.3573</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta Total bilirubin d3-d0</td>
<td>-51 [-85/-14]</td>
<td>17 [-19/64]</td>
<td>&lt;.0001</td>
<td>1.017</td>
<td>1.001-1.034</td>
<td>0.0365</td>
</tr>
<tr>
<td>Delta INR d3-d0</td>
<td>0 [-0.16/0.0]</td>
<td>0 [0.0/0.2]</td>
<td>0.0162</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta MELD d3-d0</td>
<td>-0.9 [-2.2/0.07]</td>
<td>0.3 [-0.43-1.5]</td>
<td>0.0015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta ALT d7-d0</td>
<td>-278 [-577/-88]</td>
<td>-186[-482/-18]</td>
<td>0.3841</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta Total bilirubin d7-d0</td>
<td>-98 [-140/-22]</td>
<td>6.5 [-90/117]</td>
<td>0.0072</td>
<td>1.004</td>
<td>1.000-1.008</td>
<td>0.0485</td>
</tr>
<tr>
<td>Delta INR d7-d0</td>
<td>-0.2 [-0.3/0.0]</td>
<td>0.2 [-0.2/0.4]</td>
<td>0.0004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta MELD d7-d0</td>
<td>-2.8 [-4.13/-1]</td>
<td>0.0 [-1.0/2.8]</td>
<td>0.0004</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The continuous variables are expressed using median [range IQR 1st and 3rd]. The qualitative variables are expressed using number (%).*

*De Martin et al, AASLD 2017*
• **Aim**
  – To evaluate the frequency, baseline characteristics and clinical outcomes of patients presenting AS-AIH after early i.v. corticosteroid treatment

• **Patients and methods**
  – 184 patients
    • AST, ALT >10 x, bilirubin >4 mg/dL, INR ≥1.5, without hepatic encephalopathy
    • i.v. corticosteroids
      – 1 g methylprednisolone for 1-3 days followed by 1 mg/kg/d prednisolone or
      – >1mg/kg/d prednisolone without previous methylprednisolone pulses

*Zachou et al, ILC 2017*
• Results

– 42/184 (22.8%) fulfilled the defined criteria for AS-AIH
– MELD score 19 (range 12-24)
– **Complete response** and **corticosteroids withdrawal** were more frequent in AS-AIH than not-AS-AIH (n=100)
– Only 1/42 (2.6%) died due to sepsis being on waiting list for LT, while none of the remaining required LT during follow up (median 64, range 1-187 months)

• Conclusions

– Prompt initiation of intravenous corticosteroids seems to prevent disease deterioration and the need of liver transplantation without complications

*normalization of AST/ALT, IgG levels and complete disappearance of symptoms for patients treated for at least 12 months

Zachou et al, ILC 2017
### Frequency and Nature of Side Effects (Adults)

<table>
<thead>
<tr>
<th>Prednisone-Related Side Effects</th>
<th>Azathioprine-Related Side Effects</th>
</tr>
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<tbody>
<tr>
<td><strong>Type</strong></td>
<td><strong>Frequency</strong></td>
</tr>
<tr>
<td>Cosmetic (usually mild)</td>
<td><strong>80% (after 2 years)</strong></td>
</tr>
<tr>
<td>Facial rounding, Weight gain, Dorsal hump striae, Hirsutism, Alopecia</td>
<td></td>
</tr>
<tr>
<td>Somatic (usually mild)</td>
<td>13% (Treatment ending)</td>
</tr>
<tr>
<td>Emotional Instability, Glucose intolerance, Cataract</td>
<td>Rare</td>
</tr>
<tr>
<td>Somatic (severe)</td>
<td></td>
</tr>
<tr>
<td>Osteopenia, Vertebral compression, Diabetes (brittle), Psychosis, Hypertension (labile)</td>
<td>13% (Treatment ending)</td>
</tr>
<tr>
<td>Inflammatory/Neoplastic</td>
<td>Rare</td>
</tr>
<tr>
<td>Pancreatitis, Opportunistic infection, Malignancy</td>
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</tbody>
</table>
Exploring the impact of AIH on quality of life

- **Methods**
  - EQ-5D-5L HRQOL
  - ranges from -0.281 (worst) to 1 (best)
  - data from 990 patients (39 hospitals)
  - 56% in biochemical remission
  - 55% on corticosteroids

The mean utility index was significantly lower in AIH patients, after standardization for gender and age (0.77, sd=0.23) than UK population norms (0.86, sd=0.23), t=11.4, p<0.001

**CONCLUSION:** This highlights the need for better corticosteroid-free therapy approaches and heralds future novel therapeutic trials in AIH
• 1/3 of patients were ≥60 years of age at the time of disease onset
• Similar mode of presentation
• Older patients: ↑ cirrhotic, ↑ disease progression, ↑ liver-related death
• Older patients: ↑ infections, ↑ myopathy as AE during treatment
• Similar response and relapse rates

AIH nationwide survey in Japan - subanalysis report (n=1682 pts)

AIH affects older patients
# Frequency and Nature of Side Effects (Adults)

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<td></td>
</tr>
<tr>
<td>Psychosis, Hypertension (labile)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13%                      (Treatment ending)</td>
</tr>
<tr>
<td><strong>Inflammatory/Neoplastic</strong></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis, Opportunistic infection, Malignancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rare</td>
</tr>
<tr>
<td></td>
<td>Hematologic (severe)</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>6%                      (Treatment ending)</td>
</tr>
<tr>
<td></td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>3%                      (after 10 years)</td>
</tr>
<tr>
<td></td>
<td>Hematologic /enteric</td>
</tr>
<tr>
<td></td>
<td>Bone marrow failure, villous atrophy, Malabsorption</td>
</tr>
<tr>
<td></td>
<td>Teratogenic</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>rare</td>
</tr>
</tbody>
</table>

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36. In patients with mild disease and intolerant to azathioprine, prednisolone monotherapy can be considered (II-2)

37. In all other patients, steroid-free monotherapy with azathioprine (or MMF) should be the goal of maintenance therapy. Maintenance treatment should be adapted in dose to sustain stable remission with normalised transaminases and IgG levels. The rate of relapse after prednisolone withdrawal can be reduced by application of azathioprine at a dose of up to 2 mg/kg/day (II-2)

Complete Response (CR): normal ALT and IgG levels for at least 2 years on treatment

30. Biochemical remission is defined as normalisation of IgG and transaminases. Histological remission is defined as normal histology or minimal hepatitis (HAI <4 or equivalent) (II-2)

31. Immunosuppressive treatment should be continued for at least three years and for at least two years following complete normalisation of transaminases and IgG (II-2)

32. In patients without biochemical remission, treatment should not be discontinued. In patients who have been in biochemical remission for more than two years, a liver biopsy should be considered prior to treatment withdrawal. In patients with continued histological disease activity (HAI >3), treatment should also not be discontinued (II-2)

33. Only a small minority of patients stay in remission without maintenance therapy. A trial of treatment withdrawal requires close cooperation between patient and physician. A relapse occurs most commonly within 12 months after treatment withdrawal. However, relapse may even occur many years later. Patients should therefore be closely monitored after treatment withdrawal, and surveillance continued lifelong. An increase in IgG can precede the rise of transaminases in a relapse (II-2)

34. Treatment of the relapse or flare may require steroid doses similar to the induction regimen. Earlier detection of relapse allows lower doses of immunosuppressants to re-induce full remission (II-2)

35. Patients who have received adequate immunosuppression and have relapsed during drug withdrawal, or who experienced a flare during adequate maintenance therapy should be kept on immunosuppression permanently (II-2)
Autoimmune hepatitis: current challenges and future prospects

First-line therapy

- 60 mg/d prednisolone
- or
- 30 mg/d prednisolone + 50 mg/d azathioprine

Insufficient response

- Higher dose of prednisolone and/or higher dose of azathioprine
- Taper prednisolone to maintenance dose
- Add a second-line drug (cyclosporine or tacrolimus)
- Consider liver transplantation

Favorable response

- Dose reduction or withdrawal of prednisolone or azathioprine
- Add a second-line drug (cyclosporine or tacrolimus) or (MMF instead of azathioprine)

Intolerance

- Keep maintenance dose
- Keep normal ALT and IgG

MMF, CyC, TAC
anti-TNFα, anti-CD20 anti-B cells, anti-CD3 Tregs transfer....

budesonide < 10mg/d

Decrease Of Steroid Specific Side Effects In Patients Switched From Prednisone To Budesonide (n=87)

Budesonide + AZA

- cirrhotic / PHTN ???
- steroid dependent/refractory ??
- long-term benefits ?


- induction of remission (steroid side effects)
- long-term maintenance of remission

59.3% (35/59) of patients had complete response (CR)
37% (22/59) of them having achieved CR off prednisolone

Complete Response (CR): normal ALT and IgG levels for at least 2 years on treatment
A real-world study focused on the long-term efficacy of mycophenolate mofetil as first-line treatment of autoimmune hepatitis

131 patients (AIH)
109 MMF + steroids
22 AZA + steroids

MMF-group
102/109 (93.6%) initial response
78/109 (71.6%) complete response
61/78 (78.2%) response (-steroids)
40/109 stop therapy
30/40 (75%) long term remission

Complete Response (CR): normal ALT and IgG levels for at least 2 years on treatment

Zachou K et al, APT 2016;43:1035-1047
Mycophenolate Mofetil (MMF) as Second Line Therapy – Retrospective Analysis

• MMF in n = 36 patients
  • n = 27 due to AZA intolerance
  • n = 09 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
EASL Clinical Practice Guidelines: Autoimmune Hepatitis
European Association for the Study of the Liver

EASL CPG: First Line Treatment of AIH

- **Good response**
  - Add azathioprine gradually up to 1-2 mg/kg/d
  - If azathioprine-intolerance, consider second-line therapy (usually MMF)
  - Taper steroids (ideally trial of steroid withdrawal)
  - Individualize doses (consider checking 6-TG levels) to achieve and maintain normal ALT and IgG

- **Insufficient response**
  - Consider non-compliance alternative diagnosis
  - Increase to 100 mg prednisolone i.v.
  - Manage alternative disease
  - Response
    - Insufficient response
    - Refer to specialist center for confirmation of diagnosis, LTX-evaluation and/or alternative immunosuppressives
### Alternative drug therapies for unsatisfactory responses

#### 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, (5 – 7 ng/ml)</td>
<td>hypertension, renal insufficiency, Diabetes, neuropathy</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, (3-6ng/ml)</td>
<td>Proteinuria, lipid disturbance, ulcera</td>
</tr>
</tbody>
</table>

- **Calcineurin inhibitors**
- **AZA intolerance**

**Induction of remission (steroid/AZA refractory)**
- **Maintenance therapy (toxicity ?)**

**EASL Clinical Practice Guidelines: Autoimmune Hepatitis**
- European Association for the Study of the Liver

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**Cropley A, Weltman M. Clin Mol Hepatol 2017;23:22-26**
Management of failures to standard of care

• Biologicals

  • Anti TNF
  • Anti CD 20 (Rituximab)

  • Anti B cell and anti BAFF-R (VAY736)
Anti-tumour necrosis factor (TNF) antibodies may also induce an immune-mediated liver disease resembling AIH.
### Treatment of refractory AIH with anti-TNF

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cause of infliximab treatment</th>
<th>Complications of treatment</th>
<th>Response to treatment</th>
<th>Duration of treatment</th>
<th>Number of infusions</th>
<th>Prednisolone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Cirrhosis, cyclophosphamide hepatitis, flare under ongoing standard treatment</td>
<td>Multiple infectious complications</td>
<td>Repeated prompt full remission</td>
<td>Treatment ongoing (on/off) since 2001</td>
<td>&gt;&gt;40 infusions</td>
<td>20 mg/d</td>
</tr>
<tr>
<td>2</td>
<td>Azathioprine intolerance, MMF intolerance, aggravated depression under steroids</td>
<td>Shingles</td>
<td>Initial remission, flare under ongoing treatment</td>
<td>Treatment stopped after 18 mo due to flare under treatment</td>
<td>14</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>3</td>
<td>Azathioprine intolerance, MMF intolerance, cyclophosphamide cumulative dose reached</td>
<td>Pneumonia, recurrent urinary tract infections</td>
<td>Full remission</td>
<td>Treatment ongoing for 31 mo</td>
<td>22</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>4</td>
<td>Steroid-induced diabetes and weight gain, uncontrolled disease with cirrhosis</td>
<td>Pneumonia</td>
<td>Incomplete remission with elevated IgG</td>
<td>Treatment stopped after 8 mo after pneumonia</td>
<td>9</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>5</td>
<td>Steroid-aggravated depression, weight gain</td>
<td>Recurrent herpes labialis</td>
<td>Repeated full remission</td>
<td>Treatment ongoing (on/off) for 24 mo</td>
<td>10</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>6</td>
<td>Steroid-refractory flare under treatment</td>
<td></td>
<td>Full remission</td>
<td>Stopped after 8 mo due to full remission</td>
<td>6</td>
<td>Steroids tapered out</td>
</tr>
<tr>
<td>7</td>
<td>Steroid-induced diabetes, weight gain</td>
<td></td>
<td>Full remission</td>
<td>Treatment ongoing for 15 mo</td>
<td>14</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>8</td>
<td>Azathioprine intolerance</td>
<td></td>
<td>Full remission</td>
<td>Treatment ongoing for 15 mo</td>
<td>7</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>9</td>
<td>Azathioprine intolerance</td>
<td></td>
<td>Full remission</td>
<td>Treatment ongoing for 15 mo</td>
<td>10</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>10</td>
<td>Azathioprine induced pancreatitis</td>
<td>Ocular Herpes simplex infection, recurrent urinary tract infections</td>
<td>Partial response</td>
<td>Treatment stopped after 6 mo due to allergic reaction and incomplete response</td>
<td>6</td>
<td>15 mg/d</td>
</tr>
<tr>
<td>11</td>
<td>Azathioprine intolerance</td>
<td></td>
<td>Full remission</td>
<td>Treatment ongoing for 13 mo</td>
<td>10</td>
<td>10 mg/d</td>
</tr>
</tbody>
</table>

Weiler-Norman et al. J Hepatol 2013
AIH is considered a T-cell–mediated autoimmune disease. Because B cells have been shown to play a significant role in several T-cell–mediated autoimmune diseases, some of these disorders could respond to anti-CD20 monoclonal antibodies (rituximab).

Cropley A, Weltman M. Clin Mol Hepatol 2017;23:22-26
Rituximab Treatment of AIH

Chimeric monoclonal antibody against B cell marker CD20

Cropley A, Weltman M. Clin Mol Hepatol 2017;23:22-26
Rituximab response: case reports

Cropley A, Weltman M. Clin Mol Hepatol 2017;23:22-26
Rituximab in AIH
Immunohistochemistry

A: anti CD 3 staining
B: Fox P3 + staining at baseline
C: Fox P3 + staining 48 weeks after starting rituximab

infusion reactions, bacterial infections, neutropenia, anemia, rash, fever, diarrhea, reactivation of viral infections

B-cell depletion with Rituximab demonstrates excellent laboratory efficacy at 6 months in patients with complicated AIH

- 10 patients (50% cirrhotic) with **inadequate response** or **intolerance** to all standard therapeutic combinations, or in the context of **associated autoimmune disease** wherein Rituximab had a labeled indication (RA and Wegener)

<table>
<thead>
<tr>
<th>Median (range)</th>
<th>Pre-induction</th>
<th>1 month post</th>
<th>6 months post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin µmol/L</td>
<td>23.5 (10-150)</td>
<td>18.5 (7-73)</td>
<td>11 (7-44)</td>
</tr>
<tr>
<td>INR</td>
<td>1.15 (1-1.5)</td>
<td>1.1 (1-1.2)</td>
<td>1.1 (1-1.3)</td>
</tr>
<tr>
<td>ALT IU/L</td>
<td>234 (54-688)</td>
<td>128 (34-263)</td>
<td>31 (14-90)</td>
</tr>
<tr>
<td>Albumin g/L</td>
<td>36.5 (31-47)</td>
<td>39.5 (30-42)</td>
<td>39 (35-47)</td>
</tr>
</tbody>
</table>

IgG at one month was 15.77g/l and 15.54g/l at 6 months (pre-treatment 23.48g/l).

- **Follow-up / safety**
  - **Prednisolone dose reduction** from a median of 15 (7.5-40) mg to 10 (0-20) mg
  - 2 pts developed a flare (11 months and 18 months after infusion)
  - 1 pt discontinued due to respiratory tract infections

Than et al, AASLD 2017
EASL Clinical Practice Guidelines: Autoimmune Hepatitis
European Association for the Study of the Liver

remission

Steroids ± AZA

maintenance of remission

AZA monotherapy
MMF monotherapy
Low dose Steroids ± AZA
Low dose steroids ± MMF
Budesonide ± AZA (MMF)

AZA intolerance

MMF
6-MP, 6-TG

no remission

High dose steroids ± MMF
Cyclosporin
Tacrolimus

other agents?
EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis (PBC)
EASL CPG, PBC, J Hepatol 2017;67:145-172

EASL recommends recognition that patients at greatest risk of complications from PBC are those with inadequate biochemical response to therapy, and cirrhosis.
The strongest risk factors for inadequate biochemical response to therapy are early age at diagnosis (<45y) and advanced stage at presentation (bilirubin, alkaline phosphatase, AST, albumin, platelet count, elastography) at baseline and during f/u.

EASL recommends that elevated serum bilirubin and ALP can be used as surrogate markers of outcome for patients with PBC.
Biochemical Response to UDCA at 1 Year Predicts Survival

Ursodeoxycholic acid 13-15 mg/kg/d

- Responders (n = 179)
- Nonresponders (n = 113)
- Control Population, Estimated

$P < .0001; RR, 0.4; 95\% CI, 0.3–0.5$

Defining Response to UDCA

Survival Curves for Patients Who Did (Blue) vs Did Not (Red) Meet Response Criteria

A. Barcelona criteria
- Barcelona
  - Decrease in ALP level >40% of baseline level or a normal level

B. Paris I criteria
- Paris I (all criteria met)
  - ALP level ≤3 X ULN
  - AST level ≤2 X ULN
  - Normal bilirubin level

C. Paris II criteria
- Paris II (all criteria met)
  - ALP level ≤1.5 X ULN
  - AST level ≤1.5 X ULN
  - Normal bilirubin level

D. Toronto criterion
- Toronto
  - ALP level <1.67 X ULN

Carbone M et al, Gastroenterology 2013;144:560-569
Management of cholestatic disease in 2017

Stimulation of hepatocellular secretion

Biliary \( \text{HCO}_3^- \) umbrella

↓ the vulnerability of cholangiocytes/periportalhepatocytes (hydrophobic BA)

Stimulation of cholangiocellular secretion

Bile acids

Antiapoptotic effects

Reduction of bile toxicity

↑ hydrophilicity index of biliary bile acids

anti-inflammatory action (glucocorticoid-receptor agonist activity)

Apoptosis Necrosis

35%-40% of PBC patients have an incomplete response to UDCA

Biles Acids as Enterohepatic Hormones

FXR agonists
OCA

FGF 19 mimetics

PPAR agonists

FIBRATES

---

Trauner M et al, Hepatology 2017;65(4):1393-1404
Obeticholic acid (OCA) is a semi-synthetic 6-ethyl analogue of the endogenous bile acid chenodeoxycholic acid (CDCA) that is 100 times more potent than CDCA as a FXR activator.

**FGF-19: Fibroblast Growth Factor-19**

↓ bile acid synthesis (indirectly)

↑ bile acid secretion

**Chenodeoxycholic acid (CDCA)**

Schaap et al, Nature Reviews Gastro and Hepatology 2014
Management of cholestatic disease in 2017

- ↓ bile acid synthesis (directly)
- ↑ bile acid secretion
- ↓ gluconeogenesis
- ↓ lipogenesis

↓↓ total bile acid load

BSEP: ABCB11
MRP2: ABCC2
MDR3: ABCB4
FIC1: ATP8B1

CA, Carboanhydrase
POISE Trial Design (obeticholic acid)

Randomized, double-blind, placebo-controlled, parallel-group, 12-month study of 216 patients with PBC and an inadequate response or intolerant to UDCA

<table>
<thead>
<tr>
<th>Start</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 → 10 mg titration group (n=70)</td>
<td>OCA 5 mg + UDCA</td>
<td>Titrate to 10 mg + UDCA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stay at 5 mg + UDCA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OPEN LABEL OCA + UDCA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10 mg group (n=73)</th>
<th>OCA 10 mg + UDCA</th>
<th>OPEN LABEL OCA + UDCA</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Placebo group (n=73)</th>
<th>Placebo + UDCA</th>
<th>OPEN LABEL OCA + UDCA</th>
</tr>
</thead>
</table>


patients with PBC with persistently elevated ALP above 1.67 times the upper limit of normal (ULN) or elevated total bilirubin below 2 times the ULN despite treatment with UDCA for at least 1 year
# POISE Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=73)</th>
<th>OCA Titration (n=70)</th>
<th>10 mg OCA (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56±10</td>
<td>56±11</td>
<td>56±10</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>68 (93)</td>
<td>65 (93)</td>
<td>63 (86)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>66 (90)</td>
<td>67 (96)</td>
<td>70 (96)</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>327±115</td>
<td>326±116</td>
<td>316±104</td>
</tr>
<tr>
<td>Bilirubin, μmol/L</td>
<td>12±7</td>
<td>10±6</td>
<td>11±7</td>
</tr>
<tr>
<td>UDCA use, n (%)</td>
<td>68 (93)</td>
<td>65 (93)</td>
<td>67 (92)</td>
</tr>
<tr>
<td>Daily UDCA dose, mg/kg</td>
<td>15±4</td>
<td>17±5</td>
<td>16±5</td>
</tr>
</tbody>
</table>

Data are mean ± SD where applicable.

POISE Changes in ALP and Bilirubin

↓ total bile acids
↑ FGF-19

POISE Primary Endpoint

- Composite Endpoint
  - ALP < 1.67 X ULN
  - >15% Reduction in ALP
  - Normal total bilirubin

- Primary Endpoint at Month 12
  - 5–10-mg group (46%)
  - 10-mg group (47%)
  - Placebo group (10%)
  - P<0.001 for both comparisons

oral OCA has been conditionally approved for patients with PBC in combination with UDCA for those with an inadequate response to UDCA, or as monotherapy in those intolerant to UDCA
POISE Changes in HDL and LDL Cholesterol

decrease in HDL and total cholesterol

slightly increase in LDL (first 2w)

long-term cardiovascular risk ??

OCA Adverse Events and Caveats

Pruritus
- Common, dose related

Cholesterol Changes
- Decrease in Total Cholesterol

Potential risk of chronic increase in FGF19
- Increase risk of HCC in mouse models

Cirrhotics (<20%)
disease progression, decompensation, LT, death ??

Histology (LSM unchanged)

OCA in Child-Pugh B or C patients ?

Clinical impact of lipid changes or FGF-19 elevation ?

Cost-effectiveness (≈70,000 $/year)

EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis (PBC)
EASL CPG, PBC, J Hepatol 2017;67:145-172


initial dose 5 mg; dose titration to 10 mg (according to tolerability at 6m)
“Ocaliva (obeticholic acid) is being incorrectly dosed in some patients with moderate to severe decreases in liver function, resulting in an increased risk of serious liver injury and death.”

- 19 deaths, 8 with reported causes
  - 7 cases of Child B or C cirrhosis and receiving 5 mg *daily*
  - 8 additional cases of serious liver injury without death
    - 3 cases of Child B or C cirrhosis and receiving 5 mg *daily*
- 5 cases with Child A or no reported liver dysfunction
  - 2 resolved, 3 unreported
# Peroxisome Proliferator-Activated Receptor (PPAR) Activity

<table>
<thead>
<tr>
<th>Iso-Form</th>
<th>Primary Distribution</th>
<th>Anticholestatic Mechanism</th>
</tr>
</thead>
</table>
| α<sup>1,2</sup> | Liver | • Regulates bile acid synthesis/detoxification  
• Modulates phospholipid secretion  
• Down-regulates hepatic proinflammatory genes  
• Broad anti-inflammatory effects |
| γ<sup>1,2</sup> | Adipose tissue, immune system | • Regulates adipogenesis  
• Represses transactivation of inflammatory response genes  
• Antifibrotic effect on hepatic stellate cells |
| δ<sup>3</sup> | Ubiquitous | • Regulates target genes for lipid/glucose metabolism  
• Reduces liver fat  
• Antagonizes inflammatory pathways |

**FIBRATES**

<table>
<thead>
<tr>
<th>Iso-Form</th>
<th>Primary Distribution</th>
<th>Anticholestatic Mechanism</th>
</tr>
</thead>
</table>
| $\alpha^{1,2}$ | Liver | - Regulates bile acid synthesis/detoxification  
- Modulates phospholipid secretion |
| $\gamma^{1,2}$ | Adipose tissue | anti-steatotic  
anti-inflammatory (↓ NF-kB, ↓ cytokines) |
| $\delta^{3}$ | Ubiquitous | - Regulates target genes for lipid/glucose metabolism  
- Reduces liver fat  
- Antagonizes inflammatory pathways |

- ↓ bile acid synthesis (CYP7A1 inh)  
- ↑ bile acid excretion (↑ MDR3)  

## Prospective Studies of Bezafibrate in PBC

<table>
<thead>
<tr>
<th>Author</th>
<th>UDCA dose</th>
<th>UDCA (n), UDCA+BF (n)</th>
<th>safety</th>
<th>Therapeutic outcomes of adjunct BF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakai</td>
<td>600 mg</td>
<td>13, 10</td>
<td>No side effects</td>
<td>↓ALP, GGT, IgM</td>
</tr>
<tr>
<td>Kanda</td>
<td>600 mg</td>
<td>11, 11</td>
<td>Polydipsia (n=1) - resolved</td>
<td>↓ALP and pruritus</td>
</tr>
<tr>
<td>Ohmoto 2001 &amp; 2006</td>
<td>600 mg</td>
<td>11, 6 10, 10</td>
<td>Not reported</td>
<td>↓ALP, GGT, ALT, IgM, pruritus and fatigue markers of fibrosis</td>
</tr>
<tr>
<td>Kita</td>
<td>600 mg</td>
<td>17, 22</td>
<td>No side effects</td>
<td>↓ALP, GGT, ALT, IgM</td>
</tr>
<tr>
<td>Hazzan</td>
<td>900-1500 mg</td>
<td>8, 8</td>
<td>Not reported</td>
<td>↓ALP, GGT</td>
</tr>
<tr>
<td>Takeushi</td>
<td>600 mg (12-15 mg/kg/day)</td>
<td>22, 15</td>
<td>No side effects</td>
<td>↓ALP, IgM, lipid panel</td>
</tr>
<tr>
<td>Iwasaki</td>
<td>600 mg</td>
<td>Study 1:25, 20 Study 2:12, 12</td>
<td>Study 1: abd pain (n=1); study 2: □ CPK (resolved)</td>
<td>↓ALP, GGT, IgM (study 1-no difference), □ Lipid profile</td>
</tr>
<tr>
<td>Honda</td>
<td>10-13 mg/kg/day</td>
<td>12, 19</td>
<td>Not reported</td>
<td>↓ALP, GGT, ALT, IgM, lipid profile, bile acids, gene modulation</td>
</tr>
<tr>
<td>Lens</td>
<td>13-16 mg/kg/day</td>
<td>30</td>
<td>GI side effects</td>
<td>↓ALP, GGT, ALT, pruritus</td>
</tr>
<tr>
<td>Hosonuma** (long term study for pts with PBC and hyperlipidemia)</td>
<td>12-15 mg/kg/day</td>
<td>14, 13</td>
<td>Muscle pain, leg edema, elevated creatinine in 2 subjects on BF</td>
<td>↓ALP, MRS</td>
</tr>
<tr>
<td>Freissmuth</td>
<td>13-15 mg/kg/day</td>
<td>17 pts on UDCA + BF</td>
<td>NO detrimental effect on creatinine</td>
<td>↓ALP, GGT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65% of patients normalized ALP</td>
</tr>
<tr>
<td>Corpechot</td>
<td>13-15 mg/kg/day</td>
<td>50,50</td>
<td>Elevated creatinine on BZF, normal GFR</td>
<td>57% normalized ALP, 30% normalized all liver chemistries</td>
</tr>
</tbody>
</table>
## Prospective Studies of Fenofibrate in PBC

<table>
<thead>
<tr>
<th>Author</th>
<th>Daily FF dose</th>
<th>Daily UDCA dose</th>
<th>UDCA (n), UDCA + FF (n)</th>
<th>Safety</th>
<th>Therapeutic outcomes of adjunct FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohira</td>
<td>150-200 mg</td>
<td>600-900 mg</td>
<td>7, 7</td>
<td>No AE</td>
<td>(\downarrow) ALP, GGT, IgM, pruritus and fatigue</td>
</tr>
<tr>
<td>Dohmen</td>
<td>&lt;60 kg: 100 mg</td>
<td>600 mg</td>
<td>9, 9</td>
<td>No AR</td>
<td>(\downarrow) ALP, GGT, IgM, AMA</td>
</tr>
<tr>
<td>Levy</td>
<td>160 mg</td>
<td>13-15 mg/kg/day</td>
<td>20, 20</td>
<td>Heartburn (n=2); study withdrawal</td>
<td>(\downarrow) ALP, AST, IgM, triglycerides, cytokines</td>
</tr>
<tr>
<td>Han</td>
<td>200 mg</td>
<td>13-15 mg/kg/day</td>
<td>22, 22</td>
<td>Pruritus (n=1), interruption=&gt; symptoms resolved</td>
<td>(\downarrow) ALP, GGT, AST, ALT, cholesterol and TG</td>
</tr>
<tr>
<td>Liberopoulos</td>
<td>200 mg</td>
<td>600 mg</td>
<td>4, 6</td>
<td>No AE</td>
<td>(\downarrow) ALP, GGT, ALT, cholesterol and TG</td>
</tr>
</tbody>
</table>
Bezafibrate for PBC

Randomized, double-blind, placebo-controlled, parallel-group, 24-month study of 100 patients with PBC and an inadequate response to UDCA (Paris 2 criteria)

Start

400 mg group (n=50)

Bezafibrate 400 mg

Placebo group (n=50)

Month 24

Corpechot C et al. EASL 2017
Bezafibrate Endpoints and Outcomes

Primary Composite Endpoint at 24 months

- ALP ≤ ULN
- AST & ALT ≤ ULN
- Total Bilirubin ≤ ULN
- PT ≤ ULN
- Albumin ≥ ULN

Corpechot C et al. EASL 2017
BEZURSO trial:
Bezafibrate + UDCA vs. Placebo + UDCA for PBC

- 67% of patients on BZF normalized ALP vs. 0 on placebo
- 30% of patients on BZF normalized all liver chemistries vs. 0 on placebo
- 75% improvement in itching score vs. 0% for patients on placebo
- Improvements in markers of fibrosis and liver stiffness on BZF group

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Corpechot C et al. ILC 2017 LB-01
Bezafibrate Adverse Events

Transaminases > 5 X ULN
- 1 with placebo
- 3 with bezafibrate, 2 discontinued

CPK > 5 X ULN
- 1 with bezafibrate, discontinued

Serum creatinine
- +5% with bezafibrate
- – 3% with placebo at 24 months (p < 0.01)

Hepatotoxicity
- Transient ALT/AST elevations
- Acute hepatitis (case reports)
- Chronic hepatitis (autoimmune features)
- Rhabdomyolysis, myalgias
- Class effect (12%)
- Reversible
- Not associated with ↓GFR

long-term safety ??
unknown survival benefit ??

EASL suggests currently a recommendation for therapy cannot be made

Corpechot C et al. EASL 2017
EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis (PBC)
EASL CPG, PBC, J Hepatol 2017;67:145-172

UDCA

UDCA + OCA

OCA

itching !!!

FIBRATES
Primary sclerosing cholangitis – a comprehensive review

Low UDCA dose (13-15 mg/kg/d)
✓ improves biochemistry
✓ no change in survival

Median UDCA dose (17-23 mg/kg/d)
✓ improves biochemistry
✓ trends towards improvement in survival

High UDCA dose (25-30 mg/kg/d)
✓ improves biochemistry
✓ increased rates of death/LT vs PLB

Karslen T et al, J Hepatol 2017;67:1298-1323
ALP and Risk of Death/Liver Transplant - Sweden

No long term survival difference between patients given UDCA or Placebo for 5 years. However, those who have reduced or normal ALP have longer survival rates.

OCA in Primary Sclerosing Cholangitis (AESOP)

- Phase II RCT 35 centers in the US and Italy (NCT 02177136)
  - 77 patients enrolled
- ALP ≥ 2x ULN on or off UDCA (>3 months, <20 mg/kg/day), bilirubin <2.5x ULN
- With or without IBD
- No decompensated cirrhosis
- Primary endpoint % change ALP (5-10 mg group)

clinicaltrials.gov
http://ir.interceptpharma.com/releasedetail.cfm?releaseid=1035044
OCA in PSC

Conclusion:

- **Pruritus**
  - In placebo group (n=25): 1% improvement
  - In OCA 1-3 mg group (n=25): -22% improvement
  - In OCA 5-10 mg group (n=26): -22% improvement

- **Other AEs**

- **FGF-19**:
  - Pro-proliferative and procarcinogenic

- **Bile duct, Gallbladder, Colon**

- **Early disease stage**

- **Surrogate end-points**

- **24w course Tx**

Additional Information:

- [Link](http://ir.interceptpharma.com/releasedetail.cfm?releaseid=1035044)
ROLE OF FIBRATES IN PSC
- Fenofibrate 200 mg/day + UDCA, for incomplete responders, for 6-12 months
- 13 patients enrolled
- 1 patient discontinued treatment because of muscle pains

Chazouilleres et al. Hepatology 2010; 488A
Effect of Fenofibrate on Serum ALP in Patients with PSC

- Small number of pts
- Short duration of Tx (12-24w)
- ALP improvement on Tx / relapse off Tx
- Long-term efficacy / safety data ??

24-Nor-Ursodeoxycholic acid

- Side chain-shortened C23 homologue of UDCA

Relative resistance to N-acyl-amidation (taurine / glycine)

“cholehepatic shunting”

Anti-inflammatory
Anti-fibrotic
Anti-proliferative
Nor-UDCA - Proposed Mechanism of Action in PSC

Stimulation of cholangiocellular HCO3 secretion
Bile-acid independent bile flow
Flushing of bile ducts
HCO3 umbrella

norUDCA in Primary Sclerosing Cholangitis

- Phase II RCT 38 centers in 12 countries in Europe (NCT 01755507)
  - 161 patients enrolled (159 received drug)
- ALP ≥ 1.5 x ULN off UDCA x 8 weeks (113 pt)
- With or without IBD
- No decompensated cirrhosis
- Primary endpoint % change ALP

Fickert et al, J Hepatology 2017
norUDCA in PSC

Fickert et al, J Hepatology 2017
## norUDCA in PSC: adverse events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=40)</th>
<th>norUDCA 500 mg (n=39)</th>
<th>norUDCA 1000 mg (n=41)</th>
<th>norUDCA 1500 mg (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>10%</td>
<td>7.7%</td>
<td>9.8%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12.5%</td>
<td>2.6%</td>
<td>9.8%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10%</td>
<td>0%</td>
<td>2.4%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10%</td>
<td>5.1%</td>
<td>4.9%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>17.5%</td>
<td>15.4%</td>
<td>22%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10%</td>
<td>2.6%</td>
<td>2.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Back pain</td>
<td>10%</td>
<td>2.6%</td>
<td>0%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Headache</td>
<td>7.5%</td>
<td>5.1%</td>
<td>2.4%</td>
<td>17.9%</td>
</tr>
</tbody>
</table>

Fickert et al, J Hepatology 2017
DIAGNOSTIC PROCESS

UDCA

Small Duct PSC

norUDCA

Confirmed PSC

Liver Biopsy

MRCP

+ 

- 

Confirmed PSC

ERCP

+ 

- 

Aabakken L et al. Endoscopy 2017