Managing HBV and HCV as a Comorbidity

Dimitrios Vassilopoulos
National University of Athens
School of Medicine
2nd Department of Medicine and Laboratory
Hippokration General Hospital
Athens, Greece

OUTLINE

HCV/HBV

- Basic facts for the rheumatologist

- Risk for HBV reactivation with:
  - Synthetic DMARDs
  - Biologic DMARDs

- Screening methods

- Treatment algorithm

- Monitoring during therapy
HBV-HCV: Epidemiology

~ 500 million or ~ 7% of the world population

Virgin WW et al, Cell 2009

HBV-HCV: Epidemiology

Virgin WW et al, Cell 2009
Hepatitis C virus (HCV)

- RNA virus
- Parenteral transmission
- 6 Genotypes: 1-6
- Target cell: Hepatocytes/ Lymphocytes(?)
HCV epidemiology

- Global health problem
- $\sim 2.5\%$ of the global population infected
- $\sim 180$ million chronically infected
- Accounts for:
  - 60-70% of chronic hepatitis
  - 25-50% of cirrhosis cases
- $\sim 350,000$ deaths/annually

Prevalence of infection
- $>10\%$
- 2.5-10\%
- 1-2.5%
- NA

World Health Organization 2008
Available at: http://www.who.int/ith/es/index.html.

HCV: Diagnosis - Screening

**Whom to screen**
- IVDUs
- Blood transfusion $<1992$
- High risk sexual activity
- Health care workers
- All born between 1945-65 (US)

**Screen with anti-HCV antibodies**

- **HCV RNA**
  - **HCV infection (acute/chronic)**
  - Resolved HCV infection

- **No HCV infection**
HCV: Projected disease burden

USA

Modified from Davis GL et al, Gastroenterology 2010

HCV: Natural history

Vassilopoulos & Calabrese,

Rate accelerated by:
- Long duration of infection
- Exposure > 40 yrs
- Alcohol (> 50 gm/day)
- Co-infection (HBV/HBV)
- Male sex

Rosen HR,
HCV prevalence in rheum patients

- No difference in HCV prevalence between rheumatic patients and the general population

- France:

<table>
<thead>
<tr>
<th>Early inflammatory arthritis (n=813)</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV+ 0.86%</td>
<td>0.84 %</td>
</tr>
</tbody>
</table>

*Varache S et al, Arthritis Care & Res 2011*

HCV and immunosuppression: need to worry?

- Corticosteroids
- Synthetic DMARDs
- Biologic DMARDs
  - anti-TNF
  - Rituximab
**HCV and corticosteroids**

- Short-term moderate/high dose steroid use
- Generally considered safe

---

**HCV RNA**

---

**ALT**

---

No adequate data for long-term low-dose steroid use

(? Incidence of fatty liver/fibrosis/infections …)

---

**HCV and conventional immunosuppressives**

- No increased risk for:
  - HCV reactivation (↑ HCV RNA)
  - Hepatocellular injury (↑ AST/ALT)
  - Acute liver decompensation during short-term therapy (i.e. chemotherapy, cyclophosphamide for HCV-associated cryoglobulinemia)

- No long-term safety data (risk of fibrosis/cirrhosis)
  - especially with potential hepatotoxic agents like MTX/LEF

- No adequate data in cirrhotics (infections…)

---

*Fong et al Gastro 1994*
HCV and biologics: Anti-TNF

- Rx for ~ 1 year with anti-TNF agents (ETN: 72%)
- Only 2 cases (1.3%) of confirmed/probable worsening of HCV-related liver disease

More data on liver safety in HCV patients with anti-TNFs than with any other DMARD

HCV and biologics: Rituximab

Short term use: No significant side-effects

Advanced liver disease
n=19 (Cirrhosis: n=15)
Child-Pugh Class: A=9/B=5/C=1

Long term use: ????
### HCV screening in rheum patients

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Hepatitis C serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 2008 Recommendations for the use of biologics and non-biologic DMARDs in rheumatoid arthritis (RA) (Arthritis Care &amp; Res, 2008)</td>
<td>✓ (√) (risk factors present*)</td>
</tr>
<tr>
<td>3E Recommendations for the use of methotrexate in rheumatic disorders (Ann Rheum Dis, 2009)</td>
<td>✓ (consider)</td>
</tr>
</tbody>
</table>

* IVDU, multiple sex partners in the last 6 months, health care personnel

### DMARD use in HCV rheum patients

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 2008 Recommendations for the use of biologics and non-biologic DMARDs in rheumatoid arthritis (RA) (Arthritis Care &amp; Res, 2008)</td>
<td>MTX/LEF/SSZ: Contra-indicated&lt;br&gt;Anti-TNF, RTX, ABA: Can be used in non-advanced liver disease (Child-Pugh A)</td>
</tr>
</tbody>
</table>
| Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2011 (Ann Rheum Dis 2012) | - No toxicity with anti-TNFs
Chronic HCV infection
(anti-HCV +/HCV RNA +)

Evaluation of liver disease
(stage—prognosis—indications for antiviral therapy)

- Baseline laboratory evaluation
  - AST/ALT/γGT/ALP/Bilirubin
  - Albumin
  - CBC
  - PT/INR
  - AFP

- U/S upper abdomen
- HCV genotype
- Transient elastography
- Liver biopsy*

Look for cirrhosis/portal hypertension/ HCC
Antiviral Rx decisions (1 vs. non-1)
Evaluate presence of fibrosis
Assess accurately inflammation/fibrosis

*Optional

Compensated liver Disease
(Child Pugh A)

Mild disease

Biologics
(anti-TNF, RTX, ABA)
± DMARDs
± Antiviral Rx

Moderate/severe fibrosis

Biologics
(anti-TNF, RTX, ABA)
+ Antiviral Rx

Advanced liver disease
(Child Pugh B-C)

Individualize Rx
Monitoring during therapy

HCV + patients on biologics

- ALT q3 mo
- AFP/US q6-12 mo
  (mainly in pts with fibrosis/cirrhosis)
- Transient elastography (?)

No need to follow HCV RNA levels
(unless you start antiviral Rx)

Hepatitis B virus (HBV)

Image courtesy of Scripps Research Institute
Baruch S. Blumberg (1925-2011)

- **Internal Medicine (1951-53):** Bellevue Hospital
- **Rheumatology (1953-55):** Columbia Presbyterian Hospital, NY
- Discovered the “Australia antigen” (HBsAg–1964) and the first vaccine against HBV (1969)
- Received the Nobel prize in 1976

**HBV**

- Double-stranded DNA virus
- 10 Genotypes: A-J
- Target cell: Hepatocytes
- cccDNA in hepatocyte nuclei
- Random integration into host chromosomes

**HBV: The "Rheumatology" link**

- [Image of Baruch S. Blumberg]
HBV CYCLE

Chan HLY et al, J Hepatol 2011

HBV epidemiology

- 30% (2 billion) exposed
- 5% (350 million) chronically infected
- Leading cause of:
  - Cirrhosis
  - Hepatocellular carcinoma (80%)
- ~600,000 deaths/annually

WHO Hepatitis B fact sheet

HBV prevalence

<table>
<thead>
<tr>
<th>Percentage</th>
<th>% of global population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 8%</td>
<td>45%</td>
</tr>
<tr>
<td>2-7%</td>
<td>43%</td>
</tr>
<tr>
<td>&lt;2%</td>
<td>12%</td>
</tr>
</tbody>
</table>

MMWR 2006
**Subsets - Natural History of HBV Infection (HBsAg+)**

**Initial serology**

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBe</th>
<th>Anti-HBc</th>
<th>Initial Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Chronic HBV infection</td>
</tr>
</tbody>
</table>

**Additional work-up**

<table>
<thead>
<tr>
<th>ALT</th>
<th>HBV DNA</th>
<th>Liver biopsy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>&gt; 2,000 IU/ml</td>
<td>Inflammation Fibrosis</td>
</tr>
</tbody>
</table>

**Final diagnosis**

Chronic hepatitis B (HBeAg + or -)

**Liver biopsy**

- Normal or minimal changes
- Normal

**Compensated cirrhosis**

2-6%

** Decompensated cirrhosis**

3-5%

**Hepatocellular carcinoma**

7-8%

**Death**

**20-50%**

**Diagnosis of HBV Infection**

<table>
<thead>
<tr>
<th>Initial serology</th>
<th>Initial Diagnosis</th>
<th>Additional work-up</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Anti-HBe</td>
<td>Anti-HBc</td>
<td>ALT</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Chronic HBV infection</td>
</tr>
<tr>
<td>NL</td>
<td>ND or &lt; 2,000 IU/ml</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>±</td>
<td>Resolved (past) HBV infection</td>
</tr>
<tr>
<td>NL</td>
<td>Liver + Serum ≤ 10,000 IU/ml</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>HBV vaccination</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Not exposed</td>
</tr>
</tbody>
</table>

* When performed
# Prevalence of HBV infection in rheum patients

## No difference in HBV prevalence between rheumatic patients and the general population

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient population</th>
<th>Country</th>
<th>HBsAg (+) Patients</th>
<th>Anti-HBc Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varache Arthritis Care &amp; Res 2011</td>
<td>Early inflammatory arthritis</td>
<td>France (n=813)</td>
<td>0.12%</td>
<td>0.65%</td>
</tr>
<tr>
<td>Kim DA, J Rheum 2010</td>
<td>RA</td>
<td>Korea (n=3946)</td>
<td>3.5%</td>
<td>3-4.4%</td>
</tr>
<tr>
<td>Tan J, Clin Rheum 2012</td>
<td>RA</td>
<td>China (n=476)</td>
<td>6.5%</td>
<td>7.2%*</td>
</tr>
<tr>
<td><code>Liang X et al, Vaccine 2009</code></td>
<td>RA</td>
<td></td>
<td></td>
<td>51%</td>
</tr>
</tbody>
</table>

There is no difference in HBV prevalence between rheumatic patients and the general population.

## HBV Reactivation during immunosuppression

**Circulation**

- HBV replication (liver) - \( \uparrow \) HBV DNA (serum)

**Liver**

- Hepatocytes
- Hepatocellular injury \( \uparrow \) ALT-hepatitis

**Immunosuppression**

- Mainly steroids

\( \uparrow \) HBV replication (liver) - \( \uparrow \) HBV DNA (serum)
Immunosuppression – HBV reactivation

- Definition of HBV reactivation:

**HBV DNA:**

- $> 1 \log_{10}$ (from baseline) or
- $(-) \rightarrow (+)$
- $\pm$
- $\uparrow$ ALT (> 2-3x ULN)

<table>
<thead>
<tr>
<th>Status of HBV infection</th>
<th>Reactivation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Chronic infection (HBsAg+)</td>
<td>~ 50 %</td>
</tr>
<tr>
<td>- Resolved infection (HBsAg -/anti-HBc +)</td>
<td>1-5 %</td>
</tr>
<tr>
<td>- Occult infection (HBsAg -/HBV DNA +)</td>
<td></td>
</tr>
</tbody>
</table>

Mortality rate: 5 - 40 %

Yeow W, Hepatology 2006
Hoofnagle JH, Hepatology 2009

HBV reactivation in patients receiving immunosuppressives:
Patients at risk

- Short term immunosuppression (usually <1 year)
  - Hematologic diseases (lymphomas/leukemias)
  - Neoplastic diseases (solid tumors)
  - HSCT (allogeneic)

- Long term immunosuppression (> 1 year)
  - Auto-immune diseases (RA, SLE, vasculitides...)
  - Auto-inflammatory diseases (SpA, IBD...)
  - Solid organ transplantation (kidney, heart...)
### Risk factors for HBV reactivation in patients receiving immunosuppressives

- **Risk for HBV reactivation**
  - Intensity of immunosuppression
  - HBV infection status

### Type of immunosuppression and risk for HBV reactivation in rheumatic patients

<table>
<thead>
<tr>
<th>Anti-rheumatic drug</th>
<th>HBV DNA ↑</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>++</td>
</tr>
<tr>
<td><strong>Non-biologic DMARDs</strong></td>
<td></td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>Case reports</td>
</tr>
<tr>
<td>Cyclosporine (CsA)</td>
<td>↔</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Biologic DMARDs</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>+</td>
</tr>
<tr>
<td>Rituximab (anti-B cell)*</td>
<td>++</td>
</tr>
<tr>
<td>Abatacept (CTLA-4 Ig)</td>
<td>+</td>
</tr>
<tr>
<td>Tocilizumab (anti-IL6R)</td>
<td>?</td>
</tr>
<tr>
<td>Anakinra (anti-IL1)</td>
<td>?</td>
</tr>
</tbody>
</table>

*Hematology literature
Risk for HBV reactivation

Type of immunosuppression

Low risk (<20%)
- Azathioprine
- 6-MP
- Methotrexate

Moderate risk (20-50%)
- Conventional chemotherapy
- TNF-inhibitors

High risk (>50%)
- Long course – high dose steroids
- Rituximab + chemotherapy
- New biologics (alemtuzumab)
- Allogeneic HSCT

HBV infection status

Rare
- Past HBV infection with full immunologic recovery
  HBsAg-anti-HBc+/anti-HBs- /HBV DNA-

Low risk (<10%)
- Past HBV infection with loss of protective anti-HBs
  HBsAg-anti-HBc+/anti-HBs- /HBV DNA -
  - "Occult" HBV infection
  HBsAg-anti-HBc+/anti-HBzt/HBV DNA + (liver ± serum)

Moderate – high risk (20-50%)
- Chronic HBV infection
  HBsAg+
  - Inactive carrier
    ALT: nl/HBV DNA: ND or < 2,000 IU/ml
  - Chronic hepatitis B (HBeAg + or -)
    ALT: ↑/HBV DNA > 2,000 IU/ml

HBsAg +: Chronic HBV infection

Without prophylaxis

- Anti-TNFα (n=89)
  39% (n = 5 (14%)
  Acute liver failure (4 deaths)

- Rituximabβ (n=4)
  56%

Abataceptβ
(n=4)
All patients developed HBV reactivation

---

1 Perez-Alvarez R et al, Medicine 2011 (Review of all published cases in RA, SpA, psoriasis)
2 Hematology Literature
  - Hanbali A et al, Ann Hematol 2010
  - Pi Wu et al, Ann Hematol 2010
  - Kan Ka et al, Cancer 2010
  - Mendez-Navarro J et al, Liver Int 2011
  - Chen SQ et al, Mod Diagn 2011
3 Kim Y et al, Arthritis Care & Res 2012
Chronic/past HBV infection: epidemiology

HBsAg prevalence % of global population

- ≥ 8% = high 45%
- 2-7% = intermediate 43%
- <2% = low 12%

MMWR 2006

WHO Hepatitis B fact sheet

Past HBV infection: Risk for HBV reactivation

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HBV reactivation risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional chemotherapy¹</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti-TNF²</td>
<td>1.7%</td>
</tr>
<tr>
<td>Rituximab + Chemotherapy³</td>
<td>~ 8% (2-27%)</td>
</tr>
</tbody>
</table>

- Most studies were:
  - retrospective
  - without baseline HBV DNA measurements
  - from East Asia (Rituximab-regimens)
  - in lymphoma patients (Rituximab- few data on rheum patients⁴)

¹ Lok ASF et al, Gastroenterology 1991
² Lee YH et al (Review of 9 studies, 8-668 patients)
³ Vassilopoulos D, Eur J Intern Med 2011 (review) – Only for lymphoma pts
⁴ Mitroulis I et al, Ann Rheum Dis 2013
Past HBV infection: Rituximab

- n=12
- Anti-HBc+/anti-HBs+ (n=9)
- Anti-HBc+/anti-HBs- (n=3)

- All HBV DNA: (-) at baseline
- Treated with RTX q6 months ± (DMARDs/low dose steroids) x 6-50 months (median: 13 months)
- None (0/12) developed HBV reactivation during F/U (HBsAg and HBV DNA: negative)

Mitroulis I et al, Ann Rheum Dis 2013

Screening practices for HBV among specialties (US)

- Rheumatologists 69%
- Dermatologists 42%
- Oncologists 37%

1Sine JG et al, Arthritis Care & Res, 2010 (USA – Biologics and Non-Biological)
2Sine JG et al, South Med J, 2011 (USA – Anti-TNF)
**HBV screening in rheum patients**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Hepatitis B serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 2008 Recommendations for the use of biologics and non-biologic DMARDs in rheumatoid arthritis (RA) (Arthritis Care &amp; Res, 2008)</td>
<td>√ (risk factors present*)</td>
</tr>
<tr>
<td>3E Recommendations for the use of methotrexate in rheumatic disorders (Ann Rheum Dis, 2009)</td>
<td>√ (consider)</td>
</tr>
</tbody>
</table>

* IVDU, multiple sex partners in the last 6 months, health care personnel
### DMARD use in HBV rheum patients

<table>
<thead>
<tr>
<th>Recommendations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACR 2008 Recommendations for the use of biologics and non-biologic DMARDs in rheumatoid arthritis (RA)</strong> <em>(Arthritis Care &amp; Res, 2008)</em></td>
<td>MTX/LEF/SSZ: Contra-indicated</td>
</tr>
<tr>
<td><strong>2012 Update of the 2008 ACR Recommendations for RA</strong> <em>(Arthritis Care &amp; Res, 2012)</em></td>
<td>HBsAg+ Any biologic: Can be used in non-advanced liver disease (Child-Pugh A) with antiviral treatment</td>
</tr>
<tr>
<td><strong>Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2011</strong> <em>(Ann Rheum Dis 2012)</em></td>
<td>HBsAg+ Anti-TNF: Can use with antiviral therapy</td>
</tr>
</tbody>
</table>

### How to treat HBV patients

![How to treat HBV patients diagram](image)

- **Patients starting biologic agents or high-risk immunosuppressive therapy**
  - Screen for HBV infection (HBsAg, anti-HBC, anti-HBs)
  - **HBsAg**
    - Oral antiviral treatment
  - **HBsAg Anti-HBC Anti-HBs**
    - Consider vaccination for high-risk patients
  - **HBsAg Anti-HBC Anti-HBs**
    - Vaccinated patients, no further action needed
  - **HBsAg Anti-HBC Anti-HBs**
    - Oral antiviral treatment
  - **HBsAg Anti-HBC Anti-HBs**
    - Close monitoring (HBsAg, ALT and HBV DNA tests every 3-6 months)
  - **HBsAg and/or HBV DNA**

- **Agents with low resistance rate are preferred (tenofovir, entecavir)**
  - Consider other agents (lamivudine, telbivudine, adefovir) in inactive carriers

Is this strategy successful?

Prospective study to determine the safety of anti-TNF therapy in patients with rheumatic diseases and HBV infection

Anti-TNF treated patients
n=131

Not exposed to HBV
n=79 (60%)

Chronic HBV infection
n=14 (11%)

Resolved HBV infection
n=19 (14.5%)

Previous HBV vaccination
n=19 (14.5%)

Chronic HBV infection
n=14

Inactive carriers
n=8

Lamivudine
n=8

Chronic hepatitis B
n=6

Lamivudine
n=3

Entecavir
n=2

Telbivudine
n=1

Entecavir
n=1 (liver bx showing hepatitis)

Tenofovir
n=2 (YMDD mutants)

2/14 (14%) HBV reactivation due to Lamivudine mutant strains

Vassilopoulos D et al., Ann Rheum Dis. 2010
and unpublished data
**Monitoring during therapy**

Patients on Biologics ± antiviral therapy

- **Chronic hepatitis B**
  - ALT q3 mo
  - HBV DNA q3-6 mo
  - AFP/US q6-12 mo

- **HBsAg carriers**
  - ALT q3 mo
  - HBV DNA q6-12 mo
  - AFP/US q12 mo

- **Past infection**
  - ALT q3 mo
  - HBsAg q6-12 mo
  - HBV DNA q 6-12 mo (Rituximab)

**Conclusions**

- **Screen** all rheum patients starting DMARDs for HBV (HBsAg, anti-HBc, anti-HBs) and HCV (anti-HCV)

- In HCV patients, anti-TNF and rituximab can be used without liver toxicity (be careful with cirrhotics)

- All HBsAg + patients should receive pos antiviral therapy (tenofovir, entecavir) when on biologics

- Patients with past HBV (HBsAg/-anti-HBc+) infection should be monitored carefully for HBV reactivation (especially while on RTX therapy)
Acknowledgements

This work has been supported by grants from the:

- Special Account for Research Grants (SARG), National and Kapodistrian University of Athens, Athens, Greece

- Hellenic Society for Rheumatology (ERE), Greece