Autoimmune Hepatitis

What Drug and for How Long?

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Case presentation

40 yo woman, previously healthy
• 2 weeks jaundice and fatigue
• No alcohol or drug use

Physical Exam
• Jaundice
• Tender hepatomegaly

Lab tests
• ALT 1500
• AST 1000
• Tbilirubin 10
• Alk phos 350
• INR 1.3
• SMA 1: 320
• IgG increased

Ultrasound
• Mild hepatomegaly
Liver biopsy

• Infiltration of portal tracts with lymphocytes and plasma cells, interface hepatitis, piecemeal necrosis along limiting plate and mild bridging fibrosis
Treatment Stages

Induction
• Biochemical Remission: Normalization of both transaminases (ALT/AST) and IgG

Maintenance
• For 2-3 years

Termination
• Biochemical + Histological Remission (achieved in about 25% of patients)
First-Line Therapy

- Prednisolone Monotherapy
- Prednisolone + Azathioprine
- Budesonide + Azathioprine
Predniso(lo)ne Monotherapy

Starting dose is 60 mg
- Initially higher

Tapering over 3 months
- As long as AT and IgG levels continue to fall

Maintenance dose less than 20 mg/day.

Adverse effects
- Osteoporosis, diabetes, hypertension, weight gain, cataract formation, and psychosis.
Prednisolone + Azathioprine

- Prednisolone: 30 mg/d tapered to 5-10 mg/d
- Azathioprine: 50 mg/d (US); 1-2 mg/kg/d (EU)
- Induction with prednisone alone or with AZA achieved equivalent results

Reduces steroid dose
Whether it allows faster tapering of steroids remains to be demonstrated

Most frequent side effect of AZA is cytopenia (up to 46%) due to myelosuppression.
Less common: rash, nausea, pancreatitis,

TPMT (Thiopurine Methyl Transferase) Testing
- Routine screening prior to treatment not obligatory
- Frequency of severe deficiency only 0.3%-0.5%
- Presence does not universally result in bone marrow toxicity
- Perform in patients unresponsive to AZA to detect non-compliance

Most frequent side effect of AZA is cytopenia (up to 46%) due to myelosuppression.
When to start Azathioprine: Initially vs Later?

Initial combination
• Reasona...
Budesonide + Azathioprine

- Budesonide: 9mg/d tapered to a maintenance dose of ≤6 mg / d
- Azathioprine: 50 mg/d (US); 1-2 mg/kg/d (EU)

Data are available from the European prospective trial using a Budesonide + azathioprine vs Prednisone + azathioprine
- Higher rate complete biochemical

(Manns, 2010)
Budesonide + Azathioprine

Should not be given to patients failing to respond to prednisolone
Acts via the same steroid receptor

For use in non-cirrhotic AIH only
Pharmacokinetic benefits are lost in patients with portal hypertension and

Portal vein thrombosis was reported in patients with PBC IV
Combination of prednisone and azathioprine superior to prednisone monotherapy for maintenance of remission.

Low dose maintenance with a combination of prednisone and azathioprine equivalent to azathioprine monotherapy.
Children and Adolescents

- Treatment may be different from adults since the disease in children seems to run a more aggressive course.
- Complete remission is reported in over 80% of patients.

Prednisolone
- Prominent centers use 2 mg/kg/day

Prednisolone + Azathioprine
- Some centers

Budesonide + Azathioprine
- Weight gain observed
Which particular regimen to use

Depends on a careful benefit risk evaluation for the individual patient.

Predniso(lo)n
Monotherapy
• Cytopenia

Combination Therapy
• Postmenopausal

Deficiencies
• TPMT
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Back to our patient

Started on
• Prednisone 50mg
• Azathioprine 100mg

Initial drop in liver enzymes
• AST 860
• ALT 900

6 weeks later
• AST 1100
• ALT 1400
In face of worsening liver enzymes, what is the best next step?

A. Increase prednisone to 60 mg daily or to 30 mg daily in combination with azathioprine 150 mg daily for at least 1 month.
B. Refer immediately for liver transplant evaluation
C. Add tacrolimus 2 mg twice daily to prednisone 10 mg daily and azathioprine 50 mg daily.
D. Stop prednisone; start azathioprine 50 mg daily, mycophenolate 500 mg daily, and tacrolimus 1 mg twice daily
E. Continue steroids and azathioprine at same dose and repeat liver enzymes in 6 weeks.
Management of Treatment Failure

• If complete remission is not achieved, alternative immunosuppressive agents need to be explored.
• No randomized controlled trials of alternative therapies in AIH have been conducted.

**Cyclosporin A**
- 2 to 5 mg/kg/day to achieve 100 to 300 ng/mg of blood levels
- SE: HTN, Renal insufficiency

**Tacrolimus**
- 3-5 mg/kg bid
- SE: HTN, Renal insufficiency, Diabetes, polyneuropathy

**Mycophenolate Mofetil**
- 750-1000 mg bid
- Seems to be beneficial for AZA-intolerant patients rather than patients for whom treatment has failed.
- SE: Diarrhea, Leukopenia
Biologics

- Biologics interfering with signal transduction pathways are being explored.

- Side effects of infliximab and rituximab are mainly infections.
  - Patients need to be tested for HBsAg since reactivation of hepatitis B may occur under rituximab therapy.
Biologicals

**Anti-CD3**
- Promising results in DM
- Individual cases successfully treated
- Low dose successfully induced remission in a xenoimmunized mouse model of AIH

**Tregs**
- Autoantigen-specific regulatory T cells generated and expanded in vitro from patients' own cells might offer a potentially curative approach.
Summary

• Therapies with corticosteroids
Reference


