Hepatotoxicity from Biologics?

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Hepatotoxicity from Biologics is Rare

Examples of overt hepatotoxicity with a reduction in actual hepatic function resulting from administration of biologics has been rare:

- Administration of a viscerotropism virus
  - Yellow Fever Vaccine
  - Adenovirus vector in Gene Therapy
- Infliximab – drug-induced autoimmune hepatitis
- Alpha Interferon – autoimmune hepatitis
Infliximab-Induced Autoimmune Hepatitis

- Infliximab – IgG1 murine-human chimeric monoclonal antibody which binds and neutralizes TNF
- Indicated for active RA, ankylosing spondylitis and psoriatic arthritis
- Serious hepatotoxicity estimated incidence: ~1:16,500 users per year
- 5-fold increased risk over methotrexate
Infliximab-Induced Autoimmune Hepatitis

- Onset from 2 weeks to > 1 year after start of treatment

- Liver injury predominantly hepatocellular

- Acute liver failure with need for transplant or death reported
Infliximab-Induced Autoimmune Hepatitis

• Positive anti-nuclear, anti-DS DNA, and anti-smooth muscle antibodies positive in 2/3 affected patients.

• Binding of infliximab to transmembrane TNF induces apoptosis, leading to release of nucleosomes which may trigger autoimmunity.
Biologic-induced flare of chronic hepatitis B

- In addition to being associated with rare cases of autoimmune hepatitis, Alpha interferon treatment for chronic hepatitis B is often associated with transient “flares” of chronic hepatitis B with marked further elevation of ALT.

- Interferon induces T cell cytolytic activity and natural killer cell function
Interferon-induced flare of chronic hepatitis

- Flares during interferon alpha 2b treatment of chronic hepatitis B can lead to hepatic dysfunction if a sufficient number of hepatocytes are lost during the “flare” in patients with marginal hepatic reserve.
Even mild hepatic effects from biologics rarely seen

- In a 1 year RCT involving 2 formulations of IGIV, 1 formulation was associated with statistically significant asymptomatic increases in both AST and ALT > 3x the ULN. AST and ALT remained normal in a short-term study of the same formulation.
Mild hepatic effects

- Mild reversible aminotransferases elevations during gene therapy using an adenovirus-associated virus vector.
Hepatotoxic Novel Vaccine Adjuvants?

• CBER is actively monitoring vaccine trials involving novel, non aluminum oxide based adjuvants for any occurrence of autoimmune disease, including autoimmune hepatitis.
Why is DILI Rare with Biologics?

• Number of approved drugs is much greater than the number of licensed biologics.

• Most biologics not truly xenobiotics. Although particular amino and/or RNA/DNA sequences may be unique, the building blocks occur naturally in the recipient of these products.
Degradative pathways for biologics follow rapid, largely first-order protease and nuclease enzymatic digestion, unlike the situation for drugs, which interact with oxidative and other intracellular systems.

Hepatotoxicity encountered with biologics may be explainable by some biological reaction of the protein or nucleic acid and may not resemble "idiosyncratic" DILI as seen with some small molecules.
Selected References

• Aithal G.P. Hepatotoxicity related to antirheumatic drugs. Nat. Rev. Rheumatol. 7:139-150 (2011)
