Drug Hepatotoxicity
Newer Agents

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KEYWORDS

• Drug-induced liver injury • Hepatotoxicity • Antibiotics • Antiretrovirals
• Tyrosine kinase inhibitors • Monoclonal antibodies • Anticoagulants • Antiplatelet

KEY POINTS

- Idiosyncratic hepatotoxicity is one of the most common reasons for an already approved drug being restricted or withdrawn.
- The incidence of clinically relevant hepatotoxicity from newer agents seems lower than that from older agents.
- Cases of severe hepatotoxicity have been reported and attributable to some of these newer agents, such as trastuzumab, ipilimumab, infliximab, imatinib, bosutinib, dasatinib, gefitinib, erlotinib, sunitinib, pazopanib, ponatinib, regorafenib, lapatinib, vemurafenib, crizotinib, dabigatran, rivaroxaban, clopidogrel, felbamate, lamotrigine, levetiracetam, venlafaxine, duloxetine, sertraline, darunavir, and maraviroc.

INTRODUCTION

Over the past decade, the dramatic growth in the number of new prescriptions and over-the-counter drugs has greatly improved the therapeutic armamentarium but at the expense of an increased risk of adverse drug events, in particular hepatotoxicity. Although uncommon, drug hepatotoxicity is increasingly seen in clinical practice and carries significant morbidity and mortality; approximately 30% of drug hepatotoxicity exhibit jaundice and it is one of the leading causes of acute liver failure (ALF) in the United States.[1] In addition, idiosyncratic hepatotoxicity is one of the most common reasons for an investigational drug not coming into the market and is the most common reason for an already approved drug being restricted or withdrawn. If significant liver injury is recognized during drug development, the drug would never be released into

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the market. For drugs with lower incidence of hepatotoxicity, however, liver injury is often first recognized after approval. Unfortunately, the systematic data on hepatotoxicity of newer agents are not often easily accessible, mainly due to a limited number of cases. By using available data on PubMed and the LiverTox Web site (http://livertox.nlm.nih.gov),[2] this article focuses on hepatotoxicity of select agents that have been recently introduced into the clinical arena, such as tyrosine kinase inhibitors (TKIs), monoclonal antibodies (MABs), novel or non–vitamin K oral anticoagulants (NOACs), newer antiplatelet agents, antidiabetic agents, antiepileptic drugs (AEDs), antidepressants, antipsychotics, and antiretrovirals (ARVs). In addition, hepatotoxicity due to select antibiotics commonly used in clinical practice, including amoxicillin/clavulanate, azithromycin, cefazolin, and quinolones, also is reviewed because they were frequently implicated in hepatotoxicity by the US Drug-Induced Liver Injury (DILI) Network.[1]

ANTIBIOTICS

Amoxicillin/Clavulanate

Amoxicillin/clavulanate is currently the most commonly documented cause of nonacetaminophen DILI in the United States (91 of 899 cases)[1] and Spain (59 of 461 cases).[3] The incidence of hepatotoxicity is estimated to be 1.7 to 4 of 10,000 prescriptions.[2,4–6] The mechanism of hepatotoxicity is unclear but is probably immunoallergic in origin. Certain HLA haplotypes, especially HLA class II SNP rs9274407, have been associated with amoxicillin/clavulanate hepatotoxicity, particularly in those patients who exhibit immunoallergic features.[7] The hepatotoxicity is idiosyncratic and thought primarily related to the clavulanate component, because the combination is more often associated with hepatotoxicity than amoxicillin alone.[4,6] Unlike many other DILIs, where women are at higher risk, risk factors of amoxicillin/clavulanate hepatotoxicity include older age, male gender, longer duration of exposure, and repeated courses of therapy.[4,8–10]

The mean onset of jaundice has been 16 to 37 days after the start of therapy, but a delay of up to 6 to 8 weeks has been reported (jaundice occurred after cessation of therapy in up to 50% of cases in some series).[8,11–13] Hypersensitivity features (eg, rash, fever, arthralgia, and eosinophilia) occurred in 40% to 60% of cases,[8,11] whereas interstitial nephritis and sialadenitis developed in some cases.[14] Patterns of hepatotoxicity can be either hepatocellular (approximately one-third), cholestatic (approximately one-third), or mixed injury (approximately one-third),[8,11] although case series from Belgium and France reported that cholestatic injury was the most common pattern (66%–74%).[12,13] A prospective series of amoxicillin/clavulanate hepatotoxicity from Spain reported that age was the most important determinant in the biochemical manifestation of hepatotoxicity; younger age was associated with hepatocellular injury and shorter treatment duration, whereas cholestatic/mixed injury was related to older age and prolonged amoxicillin/clavulanate therapy.[8] Typical histologic features were centrilobular cholestasis with a mixed portal inflammatory infiltrate, variable portal edema, and interlobular bile duct injury with bile duct proliferation.[6,14] In addition, granulomatous hepatitis has also been reported.[13,15] Recovery usually occurs within 1 to 4 months after cessation of therapy, although poor outcomes, including death, liver transplantation (LT), and chronic liver damage, have been reported in 9% of cases.[8]

Cephalosporins

Cephalosporins are rarely associated with DILI and cefazolin seemed the most common implicated agent in this group (ranking 6 among all drugs in the US DILI Network).[1,16]