

treatment. At day 84, both the direct and total bilirubin were within the normal range. Between day visits 8 and 28 (11th June), the patient suffered from seasonal allergy of the upper airways. On July 2010, the event resolved (between day 28 and day 84), was mild in intensity, and was **judged unlikely related to study treatment**. The event was treated with antihistamines.

#### d. FDA's Decision-Making Process in Assessing Causality

This concerns  *fingolimod* , for treating multiple sclerosis. The information is from the  *Medical Review*  for IND 022527, available from Jul. 2011 on FDA's website. The  *Medical Review*  stated that, "[o]n Day 3 of study therapy the patient developed generalized edema with symptoms of feeling bad, dyspnea ... and increase in bilateral pitting edema ... in the face, eyelids, hands, and feet."

As is evident, the FDA reviewer applied elements from the Naranjo questionnaire in assessing causality. The FDA reviewer assessed whether the adverse event of generalized edema was related to the study drug, writing that (emphasis added), "[t]he events appear to be **drug related, because it started 3 days into treatment and improved after drug discontinuation**, however, the cause of the edema remains unknown."

The FDA reviewer recommended that, in future and ongoing studies, attention should be focused on edema. To this point, the review wrote, "[f]our patients presented fluid retention/edema leading to study drug discontinuation during fingolimod treatment. ... [w]eight should be measured and 24 hour protein should be collected in patients who develop edema in

future and ongoing studies." However, it was not the case that any warning against fluid retention and generalized edema materialized in the package insert.

## IX. PARADOXICAL ADVERSE DRUG REACTIONS

### a. Introduction

An interesting aspect of adverse drug reactions is that they can take the form of a paradox. For example, a drug for preventing nausea may cause nausea, an antidepressant can increase depression, drugs used to treat bronchial spasms can induce bronchial spasms, and an anticancer drug can cause a new type of cancer.

Regarding nausea, drugs that are used to prevent nausea and vomiting may also cause nausea and vomiting. For example, aprepitant (Emend<sup>®</sup>) is used to prevent chemotherapy-induced nausea and vomiting. Although detailed information is not available on this matter, one source expressly states that this drug may induce vomiting (251), while another source clearly states that it may induce nausea (252). The existence of paradoxical adverse drug reactions can influence the clinician's decision to classify the adverse event as either expected or as unexpected.

### b. Paradox With Chemotherapy for Cancer

The phenomenon where therapy for a first type of cancer has the downstream consequence

<sup>251</sup>Package insert. Aprepitant. Cigna Pharmacy Coverage Policy; December 15, 2009.

<sup>252</sup>Package insert. Emend. Merck; March 2010.