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# Questions & Answers

*Question:* Of the two main mechanisms that have been proposed for the occurrence of drug-induced agranulocytosis, namely, immune-mediated and toxic injury, which do you believe is the more important with respect to vesnarinone and why?

*Dr Bertolet:* Of the two main mechanisms for vesnarinone-related agranulocytopenia proposed, I feel that the "toxic injury" model is the likely mechanism – mainly from a process of exclusion. There are four types of immune-mediated disease. **Type 1** represents an immediate hypersensitivity and is usually IgE-mediated. The time to onset neutropenia in patients was in the order of weeks, and would not support this process. **Type II** or cytotoxic diseases induce cytolytic actions mediated by antibody, complement, and/or cellular mechanisms. The target in type II reactions is a cell surface, and cellular damage or death is the result. There have been no documented cell death of the granulocyte-macrophage cell line. **Type III** mechanisms involve mostly antibodies forming immune complexes with antigen. Circulating complexes activate complement, attach to RBCs (which are then phagocytosed in the spleen), leave the circulation and trigger inflammation in tissue spaces (Arthus reaction), or are phagocytosed by macrophages which present antigen, release cytokines and activate B and T-cells. IgE, IgA, IgG, and IgM all form complexes with antigen. There have been some differences in cytokine expression between affected and nonaffected patients but no antibody-immune complexes have been recognized. Finally, **Type IV** hypersensitivity or cell-mediated reactions usually take longer (>12 hours) to develop and are based on activated immune cell networks. Inflammation is the basic tissue pattern, and a chronic inflammatory disease is the usual result. No inflammation has been noted on pathologic slides. The "toxic –injury" model would allow for injury to occur over a prolonged time in a certain group of patients. Vesnarinone has not shown adverse cytotoxic effects on neutrophil with direct exposure. Plasma concentrations of vesnarinone and its metabolites are unchanged in affected and nonaffected patients. I am concerned that some patients may have other concomitant medical problems that when vesnarinone is added to the mix, may produce neutropenia.

*Question:* Please expand upon the mechanism(s) of vesnarinone-induced neutropenia as a result of the findings of recent research.

*Dr Bertolet:* The toxic-injury model for vesnarinone-related agranulocytopenia is supported by the fact that vesnarinone may inhibit differentiation of HL-60 via stromal cells. However, I feel that a second offending (yet to be clearly identified) in addition to vesnarinone must be absent or present. Affected patients do have lower Epstein-Barr virus titers and higher rheumatoid factor positive rates than unaffected patients. Certain HLA phenotypes are also more likely noted in affected patients. I believe that further study will identify this agent and thereby make long-term vesnarinone administration safer.

*Question:* In your review, racial differences in therapeutic responses to heart failure treatment have been highlighted between Japanese and North American patients. Have any other diverse ethnic groups been investigated to date, and if so, what were the findings? If not, could this be an area of future research?

*Professor Sasayama:* With regard to the racial differences in therapeutic responses to heart failure treatment, there are many reports on white and black people. There are not many reports on differences between Japanese and Caucasians. I believe that racial differences in the pathogenesis and treatment of heart failure will be an important subject for future research.

*Question:* To what extent are the differences in cardiovascular disease and endpoints of heart failure treatment observed between Japanese and Caucasian patients due to lifestyle/environmental differences between these different societies? Could these lifestyle/environmental differences be exploited to justify long-term use of an inotropic agent in heart failure treatment in Western populations?

*Professor Sasayama:* The differences in cardiovascular disease between Japanese and Caucasian are more related to genetic factors rather than lifestyle/environmental differences.