

Leukotriene modifiers: New drugs, old and new reactions

As new drugs become available, the possibilities of adverse drug reactions need to be examined in a critical manner because monitoring for toxic reactions during trial periods before Food and Drug Administration approval of new drugs may be somewhat limited by numbers and scope. In this issue of *The Journal*, a case report identifies a well-established adverse drug reaction as being associated with the newly introduced leukotriene-receptor antagonist zafirlukast in the treatment of a child with mild asthma.¹ Adverse drug reactions can range from hypersensitivity to overdose to idiosyncratic reactions and/or secondary or indirect effects of drugs on physiologic function. Among the hypersensitivity reactions, immunologic drug reactions, including both immediate (Type I) hypersensitivity and autoimmune reactions (Types II, III, and IV), all have been reported.² This case highlights the possibility that a drug-induced lupus reaction or autoimmune response can be seen in an individual with asthma treated with a particular new medication. This form of drug-induced lupus associated with reactivity to histone complexes in terms of autoantibody production is an unusual reaction in patients with asthma in that this form of hypersensitivity is usually a manifestation of immunity controlled more by the CD4 T_{H1} subset, which is indicative of Type IV hypersensitivity. Because many individuals with asthma, and in particular atopic asthma, are prone to an overaggressive CD4 T_{H2} pattern of immunologic reactivity associated with atopic and asthmatic reactions, this reaction is counterintuitive. Hence the identification of the possibility of developing an alternative immunologic mechanism for the pathogenesis of drug-induced lupus in a patient with asthma is of potential pathogenetic interest.

The practical issue concerning zafirlukast-induced lupus is that it should now be examined as a possibility in those individuals in whom a lupus-like syndrome develops while they are taking this drug. It is worth mentioning that other adverse reactions have recently been described in association with zafirlukast, and this has been primarily the association of a clinical syndrome that resembles Churg-Strauss vasculitis with zafirlukast administration.^{3,4} The actual mechanism for this association is not well worked out, but what is characterized is that in patients with both Churg-Strauss syndrome associated with zafirlukast administration, as well as unexplained hypereosinophilia in the absence of a firm diagnosis of Churg-Strauss syndrome, there are common

threads concerning the unexplained eosinophilia that are found in all of these individuals reported in the literature. A number of possibilities have been raised for this interesting association. First, there is the possibility that this drug reaction may be purely a hypersensitivity reaction to zafirlukast; however, there is no evidence that such an association exists. The second possibility includes the contamination of zafirlukast with other chemicals or drugs that may induce this eosinophilia, but this explanation is also unlikely because multiple sources of production of zafirlukast cause these syndromes. A third possibility involves the unmasking of previously unappreciated and undiagnosed Churg-Strauss syndrome with tapering of steroids used for treatment of moderate to moderately severe asthma. Although this may be a contributor to unmasking some of the symptoms in some of the cases reported in the literature and by the Food and Drug Administration, it is not clear that all of the cases are specifically related to exacerbations of vasculitic syndromes or hypereosinophilia associated with steroid tapering, and furthermore, cases in which steroids had not been initially a prominent part of therapy were associated with this reaction. A final possibility suggests that an idiosyncratic hypereosinophilia, even in the face of bronchodilatation, may be seen in this circumstance. A small number of individuals may have an unusual eosinophil-based response to leukotriene-receptor blockade and/or other aspects of the biology of zafirlukast that then triggers an exacerbation of an already developing underlying condition, which may be Churg-Strauss vasculitis in some of the circumstances but may be tissue-based hypereosinophilia in other patients with adverse reactions.

There are a number of unresolved issues related to these idiosyncratic reactions to zafirlukast. First, we must ask whether this is a class-specific drug reaction in which all leukotriene-receptor antagonists may be at risk for generating this reaction. The data is not yet in on other drugs that have been used, but again these other drugs have been used in populations that are genetically distinct (ie, pranlukast in the Japanese population), as well as drugs that have not reached the wide use associated with zafirlukast (montelukast). Indeed, a case of Churg-Strauss syndrome associated with the use of pranlukast is found in the current issue of *The Journal*.⁵ Recent information transmitted to the Food and Drug Administration suggests that similar Churg-Strauss syndrome vasculitis can also be associated with use of Montelukast. It should be pointed out that cases of Churg-Strauss syndrome may also be associated with use of other asthma medications (eg, Seretide, a Serevent-Flovent combination not currently available in the United States; Romain Pauwels, manuscript in preparation).

A final point is that the true incidence of Churg-Strauss vasculitis, a very rare condition, is not well appreciated. Churg-Strauss vasculitis has not previously been associated with any scheme of adverse drug reaction or been linked in any epidemiologic or etiologic way to a potential trigger. Hence trying to understand whether these cases of Churg-Strauss vasculitis are associated with zafirlukast administration is confounded because no denominator exists for comparison in epidemiologic studies. Further immunopathogenetic study of the association of leukotriene modifiers and eosinophilia and Churg-Strauss syndrome in the small number of patients may highlight new mechanisms of the disease.

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REFERENCES

1. Finkel TH, Hunter DJ, Paisley JE, Finkel RS, Larsen GL. Drug-induced lupus in a child after treatment with zafirlukast (Accolate). *J Allergy Clin Immunol* 1999;103:533-4.
2. Adkinson NF Jr. Drug Allergy. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, editors. *Allergy: principles and practice*. 5th ed. St. Louis: Mosby; 1998. p. 1212-24.
3. Rosenwasser LJ. The vasculitic syndromes and the polyarteritis nodosa group. In: Bennett JC, Plum F, editors. *Cecil textbook of medicine*. Philadelphia: W.B. Saunders; 1996. p. 1490-5.
4. Wechsler ME, Garpestad E, Flier SR, Kocher O, Weiland DA, Polito AJ, et al. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. *JAMA* 1998;279:455-7.
5. Kinoshita M, Shiraishi T, Koga T, Ayabe M, Rikimaru T, Oizumi K. Churg-Strauss syndrome after corticosteroid withdrawal in an asthmatic patient treated with pranlukast. *J Allergy Clin Immunol* 1999;103:534-5.

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