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Cutaneous Lupus Erythematosus

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Drug-Induced Lupus Erythematosus

DIMITAR ANTONOV, MD
JANA KAZANDJIEVA, MD
DONCHO ETUGOV, MD
DIMITAR GOSPODINOV, MD
NIKOLAI TSANKOV, MD, PhD

Abstract. Among the numerous idiopathic immune-mediated diseases that can be drug-induced, such as pemphigus, psoriasis, lichen, etc., drug-induced lupus is the most widely commented upon and investigated. The terms drug-induced lupus (DIL) and drug-induced lupus erythematosus (DILE) are preferred, but other ones are also used—drug-related lupus, lupus-like syndrome, and lupus erythematosus medicamentosus.¹ This review discusses the general issues in DILE, such as pathogenic mechanisms, clinical forms, and diagnostic criteria, and provides more detailed information for some of the implicated drugs: minocycline, statins, terbinafine, etc.

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The first report to link lupus with a medication—sulfadiazin dates back to 1945.² Morrow et al in 1953 were the first to describe a definite association between hydralazine and lupus.³ Later many other reports, clinical studies, and experimental researches followed. Currently, the list of drugs associated with lupus has increased, compounds present in food and the environment have also been linked to lupus and compared to DILE, and experimental in vivo and in vitro models have been developed using medications and their reactive metabolites.

It is estimated that up to 10% of the cases with systemic lupus erythematosus (SLE) are drug-induced⁴; currently, the number of associated drugs is over 80. They are classified into four different groups according to the evidence available for causal relationship with DILE^{1,4} (Table 1). The relation to DILE for the drugs in the first group is demonstrated in well-controlled pro-

spective clinical trials and therefore is considered definite. The second group consists of drugs that are "probably associated with DILE." For those, although accumulating data is available in the form of case reports, case series, or small studies, there is no definite evidence, as is the case with the first group. For the drugs in the third group, only anecdotal reports are available. The fourth group, "recently reported drugs," was added by Pramatarov in 1998.¹ This group should be periodically revised (at least every 5 years) because the data accumulated meanwhile will direct those medications to their appropriate group.

Genetic Factors

There are two groups of genetic factors associated with the development of DILE—certain HLA alleles and drug metabolism-affecting factors. HLA-DR4 is present in 73% of the patients with hydralazine-induced lupus⁵ and this is significantly higher than in patients with idiopathic SLE. There are similar findings in minocycline-induced lupus⁶: of 13 patients, 9 were HLA-DR4 positive, 4 were HLA-DR2 positive, and all 13 had the HLA-DQB1 allele. A higher frequency of idiopathic SLE-associated HLA haplotypes, was found in Scandinavian patients with sulfasalazine-induced DILE.⁷ Presence of null alleles for C4 is also implicated with DILE.⁸

Mechanisms of DILE

The study of DILE has always been attractive, providing insight into idiopathic lupus. Successful lupus models have been established by the administration of different drugs (penicillamine, propylthiouracil, procainamide-hydroxylamine, estrogens, and others)^{9,10} to animals.

Currently, we distinguish direct and indirect mechanisms in DILE. The drugs that induce DILE through direct mechanisms (estrogens; anti-TNF therapies,

From the Department of Dermatology and Venerology, Sofia Faculty of Medicine, and the Department of Dermatology, Medical University-Pleven, Pleven, Bulgaria.

Address correspondence to: Dr. Dimitar Antonov, Department of Dermatology and Venerology, 1 St. Georgi Sofitski Str., 1431 Sofia, Bulgaria.
E-mail address: dimitar_antonov@doctor.bg