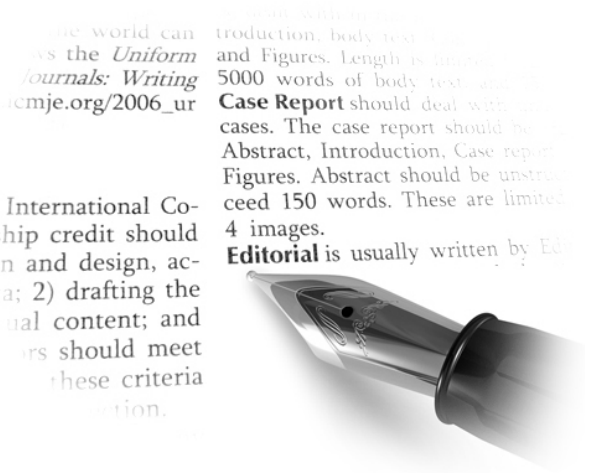

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Editorial

Dapsone therapy for immune thrombocytopenic purpura: old but still unfamiliar

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The cardinal feature of immune thrombocytopenic purpura (ITP) is developing autoantibodies directed against platelet surface antigens. Therefore, thrombocytopenia is caused by accelerated clearance of antibody coated platelets in reticuloendothelial system (RES). However, the entire picture of the disease involves more complicated pathophysiologic mechanism including cell mediated cytotoxicity and impairment of immune regulation. Further, thrombopoiesis is also affected contributing to thrombocytopenia. Accordingly, there are varieties of treatments corresponding to those pathophysiologic aspects. First line treatments intended to suppress the autoantibody production and interfere with removal of the opsonized platelets in RES include corticosteroid treatment and intravenous immunoglobulin or anti-D immunoglobulin [1]. If indicated, splenectomy is considered for refractory thrombocytopenias [1]. Options other than splenectomy include more nerve wrecking agents such as cyclophosphamide, cyclosporine A, mycophenolate mofetil [1]. Medical splenectomy like rituximab and thrombopoietin mimetics to stimulate thrombopoiesis are recently added therapies [1]. However, substantial numbers of patients still remain refractory after all available treatments have been tried. Adding to the problem, the cost of those treatments is also relatively high [2]. In this regard, dapsone is an attractive option to be adopted even by the developing part of the world with limited health resources.

In this issue of **Blood Research**, Lee *et al.* [3] reported a small retrospective single institution case series on the effect and safety of dapsone treatment in ITP. Dapsone was initially used to control systemic lupus erythematosus and HIV infection associated thrombocytopenia with some success [4-6]. This observation has been the empirical rationale of using dapsone to treat ITP. After a long time experience of its use for treating leprosy, the safety issues have already been rather thoroughly addressed. Small series of prospective studies and retrospective analysis indicates the response rate of 40 to 60%, which was a promising result considering it was achieved mostly in refractory and steroid dependent patients [2].

In the current case series, the authors present a quite different figure, at least seemingly, from those already known. As authors pointed out as the limitation of this analysis, the small number of cases and lack of statistical power, and different demographics are offered as an explanation for the difference. Thus, more data is needed to be accumulated to draw any meaningful conclusion. This report reminds us the necessity for further systematized approach in discovering a new therapeutic horizon for ITP among the readily accessible, easily affordable and safe drugs. The approach would hopefully encompass rather comprehensive activities to include studying the pharmacodynamics in more detail. In fact, one of the most repelling aspects of dapsone as to ITP treatment is that there is no proven mechanism of drug action. A popular theory involves hemolysis, a common side effect of dapsone, as the main factor. Damaged RBCs compete with platelets for the RES

macrophages to rescue the antibody coated platelets [7]. The explanation originates from the observation that the more severe the hemolysis, the better the platelet count recovery. However, the competitive clearance theory was not supported but even disputed from other studies [2, 8].

The effect now is thought to be more related to the anti-inflammatory or immune modulating effect of dapsone, which was the main reason to use it for controlling SLE and HIV associated thrombocytopenia [4, 5]. Dapsone is the first line choice of steroid-sparing long-term treatment of autoimmune blistering diseases [2]. There are bunch of experimental evidences or observations showing anti-inflammatory effects of dapsone. Dapsone is known to lower the concentration of reactive oxygen species (ROS), apparently by inhibiting the intracellular calcium mobilization necessary for ROS production [9], and suppresses the expression of Mac-1 (integrin $\alpha_M\beta_2$, CD11b/CD18) and LFA-1 (integrin $\alpha_V\beta_2$) on neutrophil and macrophage. It also inhibits the integrin mediated binding of leukocytes to ligands on the endothelial surface [9]. Cyclooxygenase and lipoxygenase pathways are inhibited and inflammatory mediators such as prostaglandin D_2, leukotriene B_4 are substantially lowered by dapsone as well as the leukocyte production of interleukin 8 and TNF-α in response to lipopolysaccharide [9]. Regarding adaptive immunity, dapsone inhibits lymphocyte transformation induced by phytohemagglutinin [9]. However, the effects on B lymphocytes are not evident and antibody production is not affected by dapsone treatment [9]. Therefore, the hypothesis is that the immune modulating effect of dapsone in recoverying platelet count is rather indirect. Overwhelming inflammatory reaction increases the chance of exposure of damage-associated molecular pattern and cross-priming adaptive immune system with cellular antigens of self-origin. Theoretically, restricting the inflammation in homeostatic boundary can trim the immune reaction to stay silent to various self-antigens. Whether the dapsone touches this realm by counteracting inflammation remains to be proven [10].

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