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Breaking a Vicious Cycle

Klaus Ley, M.D.

In this issue of the *Journal*, Moutsopoulos et al.[1] report on a patient with leukocyte adhesion deficiency type 1 (LAD1) who was successfully treated with ustekinumab, a monoclonal antibody to the p40 subunit common to interleukin-12 and interleukin-23. Patients with LAD1 have defective neutrophil adhesion, which results in few neutrophils making it into inflamed tissues. Typical locations of chronic inflammation in these patients include mucosal, skin, and periodontal sites. During 14 months of ustekinumab treatment, the patient's severe chronic periodontitis and a deep sacral ulcer largely resolved.

Blocking of p40 is unlikely to restore defective neutrophil function in patients with LAD1. So why did the treatment work so well? Normally, neutrophils continuously exit the bloodstream at mucosal sites and keep local bacteria in check (Fig. 1). In mouse models of LAD1, neutrophils cannot exit at these sites, which results in a lack of bacterial control and in accumulation of neutrophils in the blood.[2] The bacterial load at skin and mucosal sites is sensed by tissue macrophages and dendritic cells through hundreds of pattern-recognition receptors,[3] which results in the production of cytokines, including interleukin-12 and interleukin-23. In the healthy organism, neutrophils phagocytose and kill bacteria, eventually leading to the demise of the neutrophils, which are taken up by macrophages in a process called efferocytosis.[4] The uptake of apoptotic neutrophils is strongly antiinflammatory and down-regulates the production of interleukin-12[5] and interleukin-23.[6] In LAD1, this mechanism fails, because the neutrophils cannot leave the bloodstream and cannot control bacteria at barrier sites, and thus they leave interleukin-12 and interleukin-23 unchecked. Both interleukin-12 and interleukin-23 are inhibited by ustekinumab.

Previous work by the same group[7] had shown evidence of interleukin-17, a cytokine that is regulated by interleukin-23, in the gingival lesions of patients with LAD1; this provided a rationale for the experimental treatment with ustekinumab. Interleukin-23 induces interleukin-17 production in various lymphocytes, including type 17 helper CD4+ T cells[8] and γδ T cells.[6] In the gingival tissue of their patient with LAD1, Moutsopoulos et al. found elevated levels of interleukin-17–positive T cells that were negative for CD8, a phenotype consistent with both CD4+ T cells and γδ T cells. Reduced *IL17A* messenger RNA in gingival tissue as early as 3 weeks after the start of treatment suggests that ustekinumab effectively suppressed interleukin-17 production by neutralizing interleukin-23.

In patients with LAD1[9] and in mouse models of LAD1,[10] blood neutrophil numbers are strikingly elevated. This is in part caused by defective neutrophil adhesion, which leads to insufficient uptake of apoptotic neutrophils by macrophages, resulting in excessive interleukin-23 and the downstream cytokines interleukin-17 and granulocyte colony-stimulating factor.[6] Presumably, the elevated neutrophil counts might

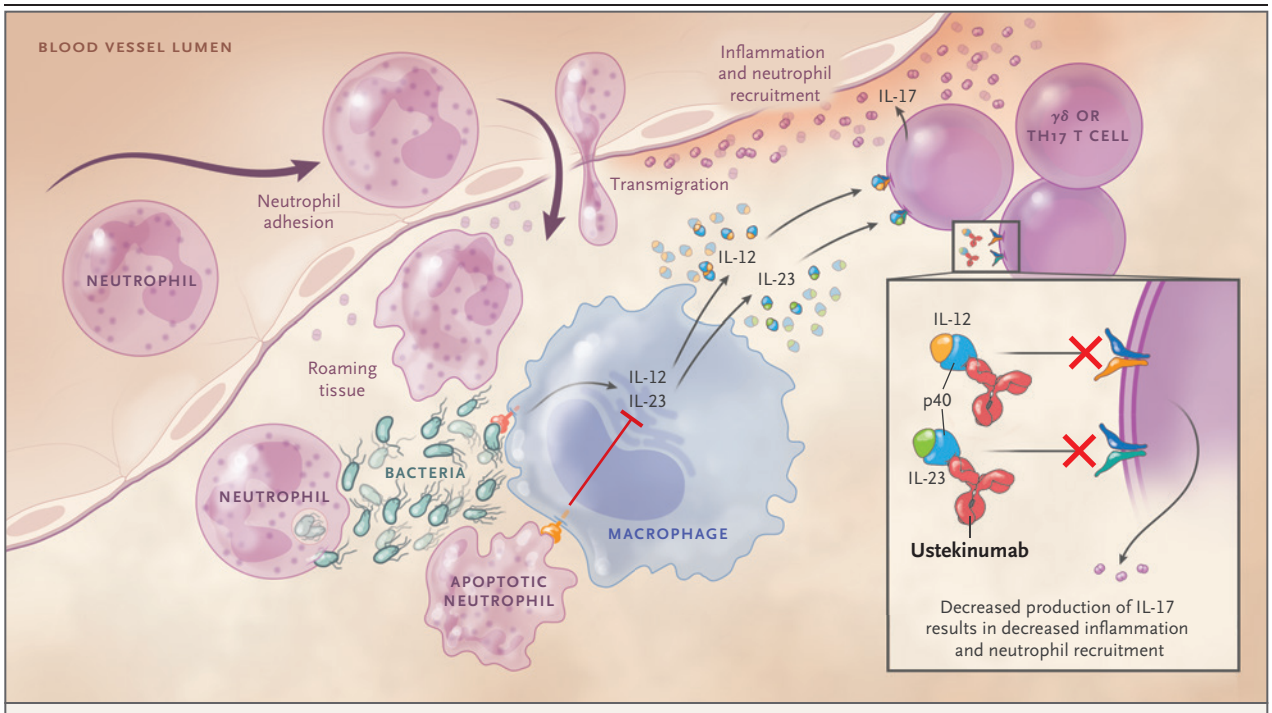

Figure 1. Inflammation Control at Mucosal and Barrier Sites.

The skin or mucosal barrier is continuously breached by some bacteria (blue rods) and other organisms that are sensed by tissue macrophages through toll-like and other receptors, resulting in the transcriptional up-regulation of interleukin (IL)–23 and IL-12. IL-23 binds the IL-23 receptor on type 17 helper (Th17) and γδ T cells and promotes production of IL-17. Macrophages also produce chemokines that cause neutrophils to adhere inside blood vessels, transmigrate, and roam the infected tissue, cleaning up infectious organisms in the process. Eventually, neutrophils become apoptotic and are taken up by macrophages through receptors for apoptotic cells, such as TYRO3, AXL, MER, BAI1, TIM-1, TIM-3, and TIM-4. This strongly inhibits secretion of IL-12 and IL-23. In patients with leukocyte adhesion deficiency type 1 (LAD1), neutrophil adhesion is defective. Therefore, neutrophils do not enter the tissue, and apoptotic neutrophils are not taken up by macrophages. Consequently, secretion of IL-23 and IL-12 continues unchecked. Ustekinumab breaks this vicious cycle by blocking the common p40 subunit of both IL-12 and IL-23.

also have been corrected by the ustekinumab treatment, which breaks this feedback loop at the level of interleukin-23. However, this was not reported.

It is clinically relevant that the proinflammatory effects of unbridled interleukin-23 and interleukin-12 at local sites drive and maintain the local inflammation. Although ustekinumab treatment cannot be expected to correct the adhesion defect, and thus neutrophils still cannot leave the bloodstream effectively and cannot control bacteria well, ustekinumab had a remarkable beneficial effect in this patient. This suggests that blocking the other proinflammatory effects of interleukin-12 and interleukin-23 is sufficient to improve wound healing and alleviate chronic inflammation. Whether this is a practical treatment for all patients with LAD1 remains to be seen. It is worth emphasizing that the patient reported here had a relatively mild form of LAD1, with 34% of CD18 still expressed. It is possible that the residual CD18 allowed some neutrophil access and some bacterial control that, together with ustekinumab treatment, improved the patient's health. Some patients with LAD1 have no CD18 expression in leukocytes. It is not known whether such patients will benefit from the proposed treatment.

In summary, Moutsopoulos et al. report an important discovery and medical advance that has the potential to meaningfully improve the management of LAD1 and perhaps other forms of leukocyte adhesion deficiency.[11] This remarkable case report suggests that blocking the interleukin-12–interleukin-23–interleukin-17 axis may benefit patients with LAD1.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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