The origins and consequences of a regulatory T cell (Treg) disorder in systemic lupus erythematosus (SLE) are poorly understood. In the (NZBxNZW) F1 mouse model of lupus, we found that CD4\(^{+}\)Foxp3\(^{+}\) Treg failed to maintain a competitive pool size in the peripheral lymphoid organs resulting in a progressive homeostatic imbalance of CD4\(^{+}\)Foxp3\(^{+}\) Treg and CD4\(^{+}\)Foxp3\(^{-}\) conventional T cells (Tcon). In addition, Treg acquired phenotypic changes that are reminiscent of interleukin 2 (IL-2) deficiency concomitantly to a progressive decline in IL-2-producing Tcon and an increase in activated, IFN\(\gamma\)-producing effector Tcon. Nonetheless, Treg from lupus-prone mice were functionally intact and capable to influence the course of disease as shown by adoptive transfer of Treg into mice with already established disease. Systemic reduction of IL-2 levels early in disease promoted Tcon hyperactivity, induced the imbalance of Treg and effector Tcon, and strongly accelerated disease progression. In contrast, administration of IL-2 partially restored the balance of Treg and effector Tcon by promoting the homeostatic proliferation of endogenous Treg. IL-2 treatment of diseased mice also strongly impeded disease progression that was most efficient by application of a repetitive regimen. In summary, an acquired and self-amplifying disruption of the Treg-IL-2 axis contributed essentially to Tcon hyperactivity and the development of murine lupus. The reversibility of this homeostatic Treg disorder provides novel and promising approaches for the selective treatment of SLE.