High mobility group box-1 (HMGB1), a pro-inflammatory cytokine, is closely associated with the pathogenesis of psoriasis. In our previous study, we explored the association of HMGB1 with psoriasis vulgaris (PV) firstly, and indicated that PV patients had increased the serum levels of HMGB1 and altered HMGB1 distribution in skin lesions. In this study, we investigated the therapeutic effects of anti-HMGB1 monoclonal antibody (mAb) in K14-vascular endothelial growth factor (VEGF) transgenic homozygous mice. We continuously injected anti-HMGB1 mAb or (PBS) i.p. once every two days for three times. We found that anti-HMGB1 mAb could effectively ameliorate the clinical skin lesions. It was shown that histopathologic changes and improvements in K14-VEGF transgenic homozygous mice after three treatments. Moreover anti-HMGB1 mAb also decreased the number of the cellular infiltration of CD3+T cells, MPO+neutrophils, and CD11c+DCs, and down-regulated the expression of IL-6, TNF-α, IFN-γ and IL-17 in psoriasis-like lesions of mice skin. In conclusion, our data suggest that HMGB1 blockade might be a promising molecular target for the psoriasis therapy.