Collagen vascular diseases (CVD) encompass a vast array of distinct clinical entities that, more or less frequently, may result in skin involvement and ulcer formation. At least three different pathogenic mechanisms may lead to skin ulcer formation in CVD. In vasculitides, the arterial wall is the seat of an inflammatory infiltrate that may result in vascular lumen obliteration, enhanced thrombus formation and downstream ischemia. In the spectrum of scleroderma-related disorders, the vasculopathy is characterized by intimal and medial fibro-proliferation, disorganized small-vessel and capillary architecture, which results in avascular areas leading to hypoperfusion, tissue ischemia and skin necrosis. Finally, CVD are frequently accompanied by the presence of anti-phospholipid antibodies that may induce arterial thrombosis with subsequent ischemia and necrosis. It is obviously important to recognize which is the pathogenic mechanism is involved in a given individual suffering of skin ulcers, in order to choose the best possible therapeutic option. Several biological markers including antinuclear antibodies (ANA), anti neutrophil cytoplasm antibodies (ANCA) and anti-phospholipid antibodies may guide the physician in the differential diagnosis. Immunosuppressive agents will be of use only in the case of ulcers secondary to active inflammation of vessel walls. Further, recent evidence indicates that biologic agents such as rituximab may be highly efficacious in controlling vasculitic manifestations.