Medium- and Large-Vessel Vasculitis

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Inflammation of large arteries such as the aorta and its major branches occurs in a number of disorders, including Kawasaki’s syndrome, Behçet’s syndrome, rheumatoid arthritis, syphilis, and tuberculosis. However, aortitis and large-vessel arteritis are characteristics of two entities—giant-cell (temporal) arteritis and Takayasu’s arteritis. These arteritides involve similar histologic abnormalities but differ in the age of onset and the vascular structures that are preferentially targeted. They share pathogenic pathways that distinguish them from other vasculitides. Cellular immune responses involving T cells, antigen-presenting cells, and macrophages are fundamental elements in giant-cell arteritis and Takayasu’s arteritis, and there is no evidence of an autoantibody component.

Giant-cell arteritis affects almost exclusively persons older than 50 years of age, and disease risk is highest among those who are 75 to 85 years of age. Disease susceptibility has been associated with northern European descent, and two thirds of those affected are women. Incidence rates reach 15 to 25 cases per 100,000 persons over the age of 50 years. Giant-cell arteritis typically causes vasculitis of the extracranial branches of the aorta and spares intracranial vessels. Transmural inflammation of the arteries induces luminal occlusion through intimal hyperplasia. Clinical symptoms reflect end-organ ischemia. Branches of the external and internal carotid arteries are particularly susceptible. Their involvement leads to the classic manifestations of blindness, headache, scalp tenderness, and jaw claudication. Vasculitis of the vertebral arteries can impair the posterior cerebral circulation and cause stroke, transient ischemic attacks, vertigo, and dizziness. Involvement of the subclavian, axillary, and proximal brachial arteries leads to the aortic arch syndrome of claudication of the arms and absent or asymmetric pulses.

Whereas giant-cell arteritis of medium-sized arteries results exclusively in narrowing and obstruction of vessels, the clinical complications of aortitis, which most often occurs in the thoracic aorta, are aneurysm formation, dissection, hemorrhage, and rupture.

In almost all patients with giant-cell arteritis, a syndrome of systemic inflammation accompanies vascular manifestations. The nonspecific symptoms include malaise, anorexia, weight loss, fever, night sweats, and depression. In patients with highly elevated acute-phase responses, such as a high erythrocyte sedimentation rate and increased levels of C-reactive protein, these symptoms are important clues to the diagnosis. Signs of systemic inflammation are also present in patients with polymyalgia rheumatica, a disorder characterized by severe myalgias and stiffness of the muscles of the neck, shoulder girdle, and pelvic girdle. About 30 to 40 percent of patients with giant-cell arteritis also have polymyalgia rheumatica. The two conditions affect the same population of patients, have the same genetic risk factors, and have similar patterns of acute-phase responses.

Takayasu’s arteritis, also known as pulseless disease, primarily involves large elastic arteries. Adolescent girls and women in their second and third decades of life are at highest risk. The syndrome is most commonly seen in Japan, Southeast Asia, India, and Mexico. In North America, the annual incidence is estimated to be 2.6 per million people. Panarteritic inflammatory infiltrates cause marked thickening of the involved ar-
tery and subsequent luminal narrowing and occlusion. Diffuse dilatation, formation of aneurysms, and thrombosis occur more frequently in Takayasu’s arteritis than in giant-cell arteritis. Clinical manifestations range from asymptomatic disease with impalpable pulses to catastrophic neurologic impairment.\textsuperscript{14,15} Most patients have diminished pulses or no pulses in the arm and blood-pressure discrepancies between the right and left arms owing to subclavian stenosis. Involvement of the carotid arteries leads to cerebral ischemia and is manifested clinically as stroke, postural dizziness, seizures, and amaurosis. Aortic regurgitation results from dilatation of the ascending aorta. The presence of hypertension most often reflects renal-artery stenosis. The long-term prognosis is frequently influenced by the presence of congestive cardiac failure associated with hypertension, aortic regurgitation, or dilated cardiomyopathy. Cough, dyspnea, chest pain, and pulmonary hypertension are present in patients with pulmonary involvement. Stenotic lesions at the origin of the renal and mesenteric arteries can complicate cases involving the abdominal aorta. As in giant-cell arteritis, vascular disease in Takayasu’s arteritis is accompanied by fever, malaise, arthralgias, myalgias, weight loss, and anemia.

Despite differences in presentation and the clinical course, giant-cell arteritis, polymyalgia rheumatica, and Takayasu’s arteritis share many pathogenic principles, and similar rules apply in the diagnostic and therapeutic approaches. The following discussion of pathogenic pathways will focus mostly on giant-cell arteritis, a reflection of the accessibility of inflamed vascular tissue that has facilitated mechanistic studies.

### The Pathogenic Model of Giant-Cell Arteritis

The diagnosis of giant-cell arteritis is established by biopsy, usually of the temporal artery. The findings are those of a panarteritis with mononuclear infiltrates penetrating all layers of the arterial wall (Fig. 1A). Typically, activated T cells and macrophages are arranged in granulomas. Multinucleated giant cells, when present, are usually close to the fragmented internal elastic lumina (Fig. 1B). Often, the intimal layer is hyperplastic, leading to concentric occlusion of the macrolumen.

Progress in understanding giant-cell arteritis has derived from three key observations. First, it is now clear that giant-cell arteritis is a T-cell–dependent disease.\textsuperscript{16,17} The CD4+ T cells that orchestrate the injury of tissues are a sine qua non in the vasculitic process. Second, T-cell activation in the nonlymphoid environment of the arterial wall requires the activation of specialized antigen-presenting cells, the dendritic cells.\textsuperscript{18} The activation of monocytes and macrophages is responsible for the systemic inflammatory syndrome in giant-cell arteritis and polymyalgia rheumatica.\textsuperscript{19} Third, the blood vessel determines the site specificity of giant-cell arteritis. Resident cells of the arterial wall respond uniquely to the immune injury mediated by tissue-infiltrating cells.\textsuperscript{20} The end result is an occlusive vasculopathy caused by the rapid proliferation of the intima or the formation of an aortic aneurysm caused by destruction of the arterial wall.

### T-Cell–Dependent Vasculitic Inflammation in Giant-Cell Arteritis

The CD4+ T cell is the critical cellular player in the vasculitic lesion.\textsuperscript{21-23} Direct evidence of a central role of T cells comes from experiments in a mouse chimera model.\textsuperscript{22} These chimeras are created by engrafting temporal-artery–biopsy specimens from patients with giant-cell arteritis into mice with severe combined immunodeficiency. Antibody-mediated depletion of tissue-infiltrating T cells in such chimeras abrogates essentially all inflammation in the implanted human tissue.\textsuperscript{22} Certain allelic variants of class II antigen-presenting HLA molecules

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**Figure 1. Giant-Cell Arteritis of the Temporal Artery.**

Panel A shows transmural inflammation of the temporal artery with granulomatous infiltrates in the media and giant cells at the media–intima border (hematoxylin and eosin, x100). The lumen is partially occluded by intimal hyperplasia. Panel B shows a close-up view of a segment of the media with several multinucleated giant cells arranged adjacent to fragments of the internal elastic lamina (hematoxylin and eosin, x200).
constitute a genetic risk factor for giant-cell arteritis and polymyalgia rheumatica, providing indirect evidence of the crucial role of antigen stimulation of CD4+ T cells. Moreover, clonally expanded populations of CD4+ T cells with identical antigen receptors have been isolated from distinct vascular lesions of the same patient. Such clonal expansion is characteristic of antigen-induced proliferation.

The antigens recognized by CD4+ T cells in giant-cell arteritis are unknown. T cells isolated from vascular infiltrates proliferate in response to extracts of temporal arteries from patients with giant-cell arteritis or polymyalgia rheumatica, suggesting the existence of a shared antigen. Infectious agents, toxins, drugs, and autoantigens in arteries would qualify, and parvovirus, influenza virus, varicellavirus, and Chlamydia pneumoniae have been suspected. Reports of material of infectious origin in temporal arteries have, however, not been corroborated.

The concept that giant-cell arteritis is the consequence of antigen-specific T cell responses in arterial tissue implies three critical events: T cells gain access to a site that they usually do not enter, an inciting antigen is accessible, and antigen-presenting cells that are capable of T-cell stimulation differentiate.

T cells leave the blood and enter tissue only if endothelial cells are activated and chemokines are produced in the tissue. In giant-cell arteritis, the port of entry is the vasa vasorum in the adventitia and not the macroendothelium. Microvessels in the inflamed arteries produce a variety of adhesion molecules that regulate leukocyte transport. Activated dendritic cells produce the chemokines CCL19 and CCL21, which have a critical role in attracting T cells and macrophages into the arterial wall. It seems that activation of endothelial cells and dendritic cells precedes T-cell recruitment to the tissue, and that the activation and differentiation of dendritic cells are key events in the pathogenesis of giant-cell arteritis.

**Vessel-Wall Inflammation**

Dendritic cells have only recently been recognized as a resident population in healthy medium-sized arteries, where they are located exclusively in the adventitia. Adventitial dendritic cells are positioned at the medial border, often outside the external elastic lamina. In healthy arteries, dendritic cells have a gene-expression profile characteristic of that of an immature cell (Fig. 2A). Immature dendritic cells have a role in maintaining T-cell unresponsiveness. In contrast to mature dendritic cells that induce T-cell responses, immature dendritic cells do not express the costimulatory molecules CD80 and CD86. If T cells encounter antigen on immature dendritic cells, they receive an inhibitory (tolerizing) signal. The function of adventitial dendritic cells may therefore lie in preventing the activation of T cells in response to antigens in the perivascular space. Indeed, adventitial dendritic cells in the temporal artery remain immature in systemic inflammatory conditions that mimic giant-cell arteritis and polymyalgia rheumatica, such as fever of unknown origin. The inhibition of T-cell immune responses at vital tissue sites by immature dendritic cells is called immunoprivilege.

Lesions in temporal arteries from patients with giant-cell arteritis contain numerous dendritic cells in the adventitia and the inflamed wall. These dendritic cells are mature and activated (Fig. 2B). They produce the inflammatory cytokines interleukin-6 and interleukin-18 and express CD86, a coreceptor required for successful interactions between T cells and dendritic cells. These mature dendritic cells have lost the ability to tolerate T cells; instead, they have acquired the ability to initiate and maintain the activation of T cells.

The activation of adventitial dendritic cells is an early event in the vasculitis. In temporal arteries from patients with polymyalgia rheumatica, which lack inflammatory infiltrates, the dendritic cells are no longer immature and have acquired the activation marker CD83. They also produce chemokines typically associated with fully mature dendritic cells (unpublished data). Activated dendritic cells typically leave tissue and migrate to lymph nodes, thereby confining the activation of CD4+ T cells to lymphoid tissues.

In polymyalgia rheumatica and giant-cell arteritis, however, activated dendritic cells remain in the artery. One mechanism that may account for this phenomenon is that dendritic cells in the inflamed artery produce the homing chemokines CCL18, CCL19, and CCL21 and express receptors for these chemokines. Large amounts of these chemokines have been identified in arteritic lesions. These chemokines are usually produced in lymph nodes, and they direct activated dendritic cells to secondary lymphoid tissues. Dendritic cells in granulomatous formations in temporal arteries in giant-cell arteritis also possess the chemokine receptor CCR7.
Because CCR7 binds CCL19 and CCL21, dendritic cells are trapped in the vascular infiltrates.  

Tissue-resident T cells induce and maintain inflammatory infiltrates by releasing interferon-γ (Fig. 3A).  

In giant-cell arteritis, interferon-γ-producing CD4+ T cells are located in the adventitia, close to resident dendritic cells. In the media, the cellular infiltrate is organized in granulomas, forming a unique spatial relation between activated T cells and macrophages. The formation of granulomas is strictly dependent on T cells and is typical of immune responses to indigestible antigens. Studies of genetically altered animals and patients with immunodeficiency syndromes have identified the critical molecular components.  

Deficiency of interferon-γ prevents the formation of granulomas. Interleukin-12, a powerful inducer of interferon-γ, can facilitate the formation of granulomas, but it is not essential. Interferon-γ is a key cytokine in the arteritic lesion of giant-cell arteritis, and it is absent from tissues affected by polymyalgia rheumatica, which do not have fully developed vascular infiltrates. Interferon-γ mediates most of its inflammatory effects by inducing macrophages to perform a broad spectrum of effector functions. Interestingly, interleukin-12 is missing from the vascular lesions of giant-cell arteritis, indicating a role for alternative interferon-γ–inducing cytokines.

The mechanisms of injury in Takayasu’s arteritis are similar to those of giant-cell arteritis and include the activation of macrophages by stimulated T cells. However, in Takayasu’s arteritis, T cells may have additional effector functions, such as releasing the pore-forming protein perforin, which could directly contribute to the structural damage incurred by the aortic wall.

Granulomatous reactions can encapsulate and wall off immunogens, but they cause extensive tissue damage. Tissue necrosis resulting from released lytic enzymes is characteristic of Wegener’s granulomatosis and Churg–Strauss vasculitis. Fibrinoid necrosis and destruction of the arterial wall are hallmarks of nongranulomatous vasculitides, such as panarteritis nodosa. Necrosis is not a feature of giant-cell arteritis, and its presence should raise doubts about the diagnosis of giant-cell arteritis. Thinning of the temporal-artery wall has been described, and the end stage of giant-cell aortitis may be complicated by the formation and rupture of an-
eurysms. However, the release of lytic enzymes is not sufficient for the overt digestion of arterial-wall components in most patients. The exception is the fragmentation of the internal elastic lamina, a process often associated with the appearance of multinucleated giant cells.

Screening for genes that are differentially expressed in inflamed temporal arteries has been fruitful in deciphering the effector mechanisms of arterial injury. Many genes that are overexpressed in inflamed arteries participate in pathways of oxidative stress. Lipid peroxidation mediated by reactive oxygen intermediates is an important pathway of arterial-wall damage (Fig. 3B). The chief target of the oxidative attack is medial smooth-muscle cells. Nitrosative stress resulting from the accumulation of nitrated proteins primarily affects endothelial cells lining newly formed capillaries in the arterial media and is mediated by the concerted action of endothelial nitric oxide synthase and reactive oxygen intermediates produced by medial macrophages. Protein nitration can also alter intracellular signaling cascades and modulate cellular function. In healthy blood vessels, the media is free of capillaries and is inaccessible to inflammatory cells. Endothelial activation in inflammation-induced neocapillaries, brought about by oxidative stress, can increase the recruitment of lymphocytes and macrophages and aggravate inflammation.

Oxidative stress occurs in the medial layer but not in the adventitia or the intima, probably because only macrophages in the media produce reactive oxygen intermediates. The function of macrophages in the arterial wall is highly organized. Macrophages committed to restricted effector functions are confined to distinct regions, a finding that strongly indicates that the artery itself guides the inflammatory process. Signals derived from matrix components in microenvironments of the artery may regulate selective homing or in situ differentiation of effector macrophages.

Oxygen-derived free radicals and their metabolites injure tissue through several mechanisms; the most important is oxidation of membrane lipids, resulting in structural disintegration and cell death. Reactive oxygen intermediates are not always cytotoxic; they can also alter cellular function by disrupting intracellular signaling cascades. Activation of gene transcription as an outcome of oxidative stress is exemplified by the induction of the keto-reductase aldose reductase in the medial layer of inflamed temporal arteries. In vivo, the expression of aldose reductase in medial smooth-muscle cells closely mirrors the distribution of the toxic aldehyde 4-hydroxy-2-nonenal, and 4-hydroxy-2-nonenal upregulates the transcription of aldose reductase in vitro. The induction of this enzyme appears to be a protective mechanism; aldose reductase detoxifies the toxic aldehydes that are produced by oxidative stress. Blockade of aldose reductase in vivo promptly increases tissue levels of 4-hydroxy-2-nonenal and induces apoptosis of smooth-muscle cells. This example illustrates the balance between destructive and protective mechanisms that is characteristic of the pattern of response to injury in giant-cell arteritis. Intimal hyperplasia is favored over aneurysm formation.

**Figure 3 (facing page). Adaptive Immune Responses in Vasculitis and the Consequences of Arterial-Wall Injury.**

In Panel A, activation and trapping of dendritic cells in the arterial adventitia generate the conditions required for the recruitment and stimulation of antigen-specific T cells. CD4+ T cells that enter the microenvironment of the arterial wall interact with dendritic cells and begin secreting cytokines. Interferon-γ is a critical cytokine that regulates the differentiation and function of macrophages. The functional commitment of the macrophages in the vascular infiltrates is closely linked to their location in the arterial wall. Macrophages in the adventitial layer supply the inflammatory cytokines interleukin-1 and interleukin-6. Macrophages in the media secrete metalloproteinases and play a critical part in oxidative injury through the production of reactive oxygen intermediates. Three aspects of oxidative damage in the media are shown in Panel B. Protein nitration occurs in endothelial cells lining neocapillaries. Toxic aldehydes are formed in the process of lipid peroxidation, and smooth-muscle cells undergo apoptosis. In parallel, reactive oxygen intermediates also trigger cellular activation, as exemplified by the induction of aldose reductase. The response of the artery to injury is shown in Panels C and D. Arteritis does not necessarily result in luminal stenosis and may proceed without compromising blood flow (Panel C). In patients with ample production of platelet-derived growth factor and vascular endothelial growth factor, rapid and exuberant intimal hyperplasia ensues, causing lumen-occlusive arteritis (Panel D). Accordingly, the clinical presentation of arteritis may or may not include ischemic complications.

**Response of Arteries to Immune-Mediated Injury**

Hemorrhage and the formation of aneurysms in extracranial arteries are not features of giant-cell arteritis. Instead, the most feared complications result from ischemia. Blindness is caused most often by
Table 1. Therapeutic Applications for Pathogenic Pathways in Giant-Cell Arteritis.

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<th>Therapeutic Approach</th>
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<td>Vascular stenosis caused by intimal hyperplasia</td>
<td>Use inhibitor of platelet aggregation for severe but incomplete occlusion Inhibit myofibroblast proliferation</td>
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<tr>
<td>Intimal proliferation supported by neoangiogenesis</td>
<td>Suppress neovascularization</td>
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<td>Oxidative injury of medial smooth-muscle cells</td>
<td>Inhibit the formation of reactive oxygen intermediates</td>
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<tr>
<td>Activation of smooth-muscle cells by oxidative injury</td>
<td>Inhibit the formation of reactive oxygen intermediates</td>
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<td>Secretion of interferon-γ, the critical regulatory cytokine in the lesion</td>
<td>Use aspirin to down-regulate interferon-γ production Block interferon-γ–inducing cytokines</td>
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<td>Triggering of adventitial dendritic cells early in arteritis</td>
<td>Deplete mature dendritic cells or inhibit dendritic-cell function Neutralize dendritic-cell–mediated T-cell stimulation</td>
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<td>Innate immune responses directed by systemic inflammation</td>
<td>Inactivate macrophages Inhibit nuclear factor-κB with corticosteroids</td>
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<td>Systemic inflammation preceding and independent of vascular inflammation</td>
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HETEROGENEITY OF CLINICAL DISEASE AND ITS PATHOGENIC CORRELATES

Pathogenic studies have shown that giant-cell arteritis is a heterogeneous syndrome, with clinical phenotypes correlating with different patterns of immune response. The most distinct variant is polymyalgia rheumatica, in which vascular inflammation remains undetectable. In polymyalgia rheumatica, adventitial dendritic cells are mature and both interleukin-1 and interleukin-6 are detectable, but interferon-γ–producing T cells are not recruited into vascular tissue. Interestingly, the systemic inflammatory component of giant-cell arteritis and that of polymyalgia rheumatica are indistinguishable and are characterized by the production of large amounts of macrophage-derived inflammatory cytokines.

A clinically important subgroup of patients with medium- and large-vessel vasculitis consists of those at risk for ischemic complications. Arterial stenosis is closely associated with intimal hyperplasia, driven by growth and angiogenic factors. Another subgroup of patients do not have luminal stenosis — the arteritis proceeds without eliciting intimal growth (Fig. 3C). Mechanisms underlying the variability of the response of the artery to injury are not fully understood, but the nature of T-cell responses appears to regulate the extent of intimal growth factor. This growth factor also derives from macrophages, specifically those at the media–intima junction. Outgrowth of the intima could not occur without accompanying angiogenesis. Medium-sized arteries receive oxygen through either diffusion from the macrolumen or the capillary network of the vasa vasorum in the adventitia. In arteries affected by giant-cell arteritis, microvessels emerge in the media and the hyperplastic intima (Fig. 3C). The topical arrangement is strictly regulated and forms a ring-like structure in the proximal intima. The level of production of vascular endothelial growth factor but not fibroblast growth factor 2 in the vasculitic lesion correlates closely with the number of neocapillaries. Vascular endothelial growth factor derives from macrophages and multinucleated giant cells. Thus, a coordinated action of the arterial wall and the invading immune cells drives the hyperproliferative response of the intima.
Morphologic hallmarks of the temporal-artery–biopsy specimens and tissue cytokine profiles could be useful in risk stratification. In patients without luminal stenosis, the diagnosis relies heavily on arterial biopsy, because imaging procedures such as ultrasonography depend on blood-flow abnormalities and lack the sensitivity to detect subtle inflammation of arterial walls. The diagnosis of nonstenosing giant-cell arteritis in vascular beds that are not accessible for a routine biopsy, such as the subclavian, axillary, or vertebral arteries, may require positron-emission tomography with fluorodeoxyglucose. This method has high sensitivity for the detection of metabolic changes in the arterial wall. Magnetic resonance imaging and computed tomography are useful, but they may not always be sensitive enough to detect arterial-wall abnormalities.

**THERAPEUTIC IMPLICATIONS**

Systemic inflammation and the arterial-wall lesions in giant-cell arteritis and polymyalgia rheumatica are intimately linked, but they may require different therapeutic approaches (Table 1). Within the two disease components, a myriad of mediators has emerged, each of which contributes to different aspects of the systemic or vascular pathogenesis. These mediators are promising targets for a tailored strategy in the treatment of medium- and large-vessel vasculitides (Table 2).

**OPTIMIZING CORTICOSTEROID TREATMENT**

The production of inflammatory cytokines by the innate immune system is exquisitely sensitive to the immunosuppressive action of corticosteroids. Inhibition of the nuclear factor-κB pathway by corticosteroids disrupts a multitude of inflammatory signals, which explains why symptoms of systemic inflammation caused by stimulation of the innate immune system are highly sensitive to corticosteroids. The immune response in the artery, however, is relatively resistant and persists despite long-term therapy with corticosteroids. These two components of giant-cell arteritis may require different therapeutic interventions (Table 1). The ability of corticosteroids to prevent blindness may result from a reduction in vascular-wall edema or the disruption of the triggering of dendritic cells in the arterial adventitia. Given the limited efficacy of corticosteroids in eliminating vessel-wall inflammation, the value of currently used regimens of corticosteroids needs to be readdressed.

**COMBINATION THERAPY**

It is unlikely that a single therapeutic intervention can abrogate giant-cell arteritis or suppress both the systemic inflammation and the vascular abnormalities. Instead, different strategies must be used for the multiple pathogenic pathways operational in the innate and adaptive immune systems. Suppressing luminal occlusion by modulating pathways of the arterial response to injury may be the next best step in improving the management of large-vessel vasculitides. Possible interventions include the prevention of oxidative injury, down-regulation of myofibroblast proliferation, and modulation of capillary formation in the arterial wall (Table 2).

**ASPIRIN**

Although thromboembolic occlusion is not a mechanism in giant-cell arteritis, therapeutic benefit has been reported with the use of low-dose aspirin. Prevention of platelet aggregation is potentially ef-
effectiv, even in patients with partial luminal occlusion. In addition, a potent antiinflammatory action of aspirin has been described in the mouse chimera model of giant-cell arteritis. Aspirin interferes with the transcriptional activation of the interferon-γ gene, a mechanism of action that may be particularly useful in inhibiting T-cell function in the granulomatous infiltrates.

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