Review

New therapeutic targets in giant-cell arteritis. Considerations based on the current pathogenic model and the availability of new therapeutic agents

E. Lozano, M. Segarra, A. García-Martínez, G. Espígol-Frigolé, J. Hernández-Rodríguez, M.C. Cid

Department of Systemic Autoimmune Diseases, Clinical Institute of Medicine and Dermatology, Hospital Clínic, University of Barcelona, Institut d'Investigacions Biomèdiques, Barcelona, Spain.

Ester Lozano, PhD;
Marta Segarra, PhD;
Ana García-Martínez, MD;
Georgina Espígol-Frigolé, MD;
José Hernández-Rodríguez, MD;
Maria C. Cid, MD.

This study was supported by the Ministerio de Educación y Ciencia and Fondo Europeo de Desarrollo Regional (FEDER) (SAF 05/06250 and SAF 08/2011) and Marató TV3 (06/0710). G. Espígol-Frigolé and M.C. Cid are supported by the Instituto de Salud Carlos III.

Please address correspondence to: Maria C. Cid, MD, Department of Systemic Autoimmune Diseases, Clinical Institute of Medicine and Dermatology, Hospital Clínic, Villarroel 170, 08036-Barcelona, Spain.
E-mail: mccid@clinic.ub.es

Received on June 3, 2008; accepted in revised form on June 21, 2008.

Clin Exp Rheumatol 2008; 26 (Suppl. 49): S142-S151.

Key words: Vasculitis, pathogenesis, cytokines, biologic therapies.

Conflict of interest: Dr. M.C. Cid has received a research grant from Centocor, Inc.; all the other co-authors have declared no competing interests.

1. Why search for new therapeutic targets in giant-cell arteritis?

Giant-cell arteritis (GCA), a granulomatous arteritis of the elderly has been considered the paradigm of a glucocorticosteroid sensitive disease (1, 2). Response to treatment is often spectacular within hours or days and, based on this observation, quick and complete disappearance of symptoms has been considered a requirement to admit the diagnosis of GCA when histological confirmation is not available (3, 4). Why, then, is there a need for alternative or adjuvant therapies in GCA? In spite of the initial response to glucocorticoids experienced by the majority of patients, the management of GCA still faces a number of unresolved challenges (2):

1) Visual impairment, commonly due to anterior ischemic optic neuritis, still occurs in 15-20% of patients in recent series (5-7). When visual loss is established, prompt glucocorticosteroid treatment is only followed by objective improvement in the visual field in 4% of involved eyes (8, 9). In 10-17% of patients who present with visual symptoms, vision continues to deteriorate during the first 1-2 weeks after the initiation of glucocorticosteroid treatment (10-11).
2) In spite of an apparent response to glucocorticosteroids, significant aortic dilatation or aneurysm develops in 22.5% of patients after a median follow-up of 5.4 years (12). An undetermined percentage of patients, ranging between 5-15% in retrospective series develop large vessel stenosis and limb claudication during follow-up (13, 14). Whether this complication is entirely related to GCA or is also due to atherosclerotic changes has not been clearly elucidated.
3) While inducing remission with high glucocorticoid doses is easily achieved by the majority of patients, remission maintenance is more problematic and long-term response to treatment is quite heterogeneous. Approximately 10-15% of patients cannot reduce corticosteroids below 10-15 mg/day without experiencing disease flares or smouldering activity (15). About 40-60%, even being able to taper corticosteroids to physiologic or near to physiologic levels cannot tolerate complete withdrawal after 2-3 years (16-18). Corticosteroid-related adverse events cumulate over the years and about 86% of patients experience at least one side effect over a median follow-up period of 10 years (16). It is then clear that current therapy is not sufficient to abrogate disease activity and its consequences in a substantial proportion of patients.

Over the past 15 years and based on the progress made in understanding the pathogenesis of chronic inflammatory disorders, a new generation of treatments has emerged. Biologic therapies are aimed to target specific mediators who are thought to play a role in disease pathogenesis or disease chronicity. Search for therapeutic targets requires, then, a better understanding of the pathogenic mechanisms involved in GCA. In this review we discuss potential points of intervention based on the pathogenesis model for giant-cell arteritis assembled over the past recent years (19, 20).

2. Targeting key events in the pathogenesis of giant-cell arteritis

2.1 Early events

Interfering with early events before irreversible damage or excessive vascular remodelling occurs would be a major achievement in the treatment of GCA (Fig. 1). However, even if early intervention was possible, identifying GCA at this point may not be feasible since, unfortunately, patients usually seek medical attention when lesions are fully developed. Identifying and intervening in the early steps in the development of the disease would be particularly useful for the subset of patients followed and treated for polymyalgia rheumatica (PMR) who may eventually develop GCA (21).

2.1.1 Triggering agents

It is currently believed that GCA occurs as a consequence of an antigen-specific immune response against still unidentified antigens present in the artery wall (19, 20, 22). This hypothesis is supported by several experimental data including detection of activated dendritic cells (22, 23), oligoclonal expansion of CD4 positive T cells in lesions (24), and disruption of inflammatory infiltrates in temporal arteries engrafted onto mice with severe combined immunodeficiency (SCID) by anti-dendritic cell monoclonal antibodies (23). Since latent viruses and other intracellular pathogens may lead to large vessel vasculitis (25), several investigators have searched for pathogens including human herpes virus, B19 parvovirus, and Chlamydia in GCA specimens (26-28). The examples of *Helicobacter pylorii* or *Tropheryma whipplei* illustrate how identification of a causative pathogen may dramatically change and improve the treatment of chronic inflammatory diseases. However, the search for infectious agents in GCA has been unsuccessful, leading to inconsistent results (26-28).

2.1.2 Dendritic cell activation

As in other chronic inflammatory diseases, innate immunity may also play a role in modulating disease severity or disease recurrence. It has been demonstrated that there is a population of resident immature dendritic cells in the adventitia of normal arteries which need to be activated to become mature antigen presenting cells (23). Vascular resident dendritic cells bear Toll-like receptors (TLRs) in vessels involved by GCA, particularly TLR2 and TLR4 (23). It has been shown that stimulating TLR4 with LPS may result in induction of a mature phenotype in temporal artery dendritic cells as exemplified by expression of CD86, as well as induction of chemokines and chemokine receptors able to retain dendritic cells in lesions and chemoattract lymphocytes (23, 29). Activation of dendritic cells seems, then, to be a very initial pre-requisite for subsequent antigen presentation and triggering of an antigen-specific adaptive immune response. TLR4 may also have endogenous ligands. In this regard, it has been recently demonstrated that MRP8 (S100A8), a protein released by early infiltrating phagocytes and down-regulated in tissue macrophages, may function as a TLR4 ligand (30). MRP8 is expressed by leukocytes surrounding *vasa vasorum* and neovessels in GCA lesions, indicating their recent recruitment into lesions and suggesting that pro-inflammatory functions of MRP8 may be relevant in early steps of vascular inflammation (31). Supporting this concept, MRP8 is one of the genes up-regulated in spared temporal arteries from patients with GCA (32) and in temporal arteries from patients who will undergo a relapsing outcome (33). Interference with TLR4 signalling is presently under investigation in the field of sepsis and cardiovascular disease (34, 35).

2.1.3 CD4$^+$ T cell depletion

Inflammatory infiltrates in GCA are mainly composed of CD4$^+$T cells and macrophages (20). Treating SCID mice bearing engrafted human temporal arteries from patients with GCA with antibodies directed against human T cells has been shown to decrease the production of Th1 cytokines in engrafted arteries (36). Therapeutic depletion of lymphocytes with the humanised monoclonal antibody alemtuzumab (anti-CD52, CAMPATH-1H) has been used to treat renal allograft rejection (37) and

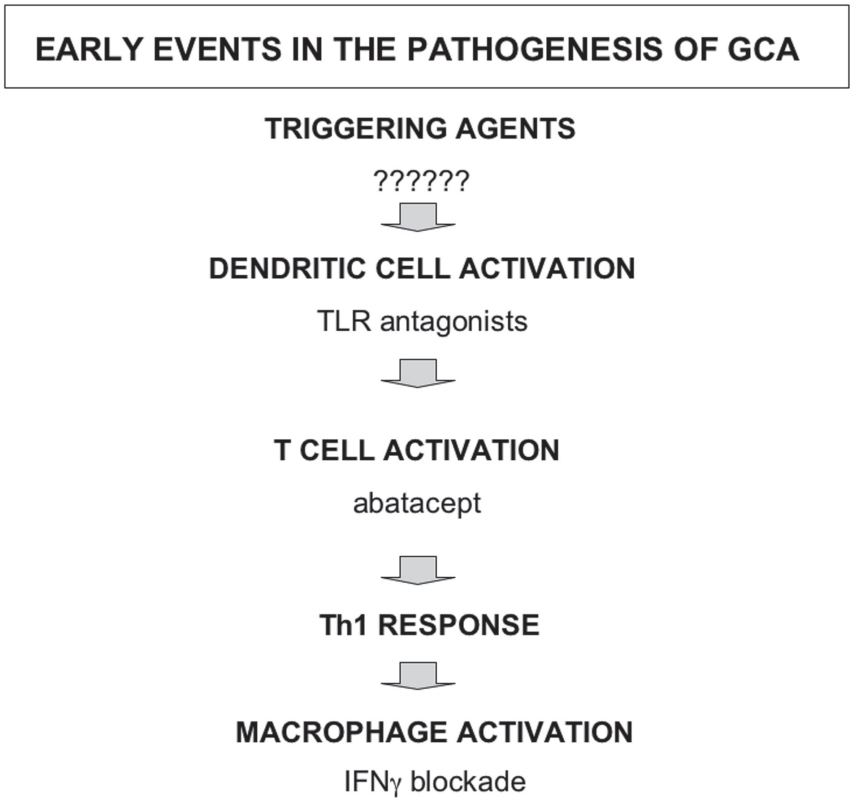

Fig. 1. Summary of early events in the pathogenesis of giant-cell arteritis (GCA) with potential points of intervention.

systemic vasculitis including microscopic poliangiitis and Wegener's granulomatosis refractory to conventional therapies (38). CD52 is present in lymphocytes and macrophages but a major effect of alemtuzumab is T-cell depletion, since recovery of CD4 T cells is usually delayed and incomplete. While this treatment has been complicated with severe infections it appears that it is able to induce much longer sustained remissions than standard immunosuppressive agents in patients with necrotising vasculitis (38). Lymphocyte depletion may be an excessively aggressive therapy for patients with GCA and the risk/benefit balance of this approach may not be appropriate.

2.1.4 B-cell depletion

It has been considered that B cells do not have any role in the pathogenesis of GCA (20, 39). However, although B cells are scarce, they are not absent from GCA inflammatory infiltrates (22). Response of GCA to anti-CD20 therapy with rituximab has been anecdotally reported (40). The putative role of B cells needs to be explored before B-cell depleting therapies are considered for patients with GCA.

2.1.5 Interfering with T-cell co-stimulation

While B or T cell depletion have not been considered for the treatment of GCA, interfering with T cell co-stimulation by antigen-presenting cells has drawn some interest. Abatacept, a fusion protein consisting of an Ig Fc fragment fused to the extracellular domain of CTLA efficiently interferes with interactions between CD80/86 molecules on antigen-presenting cells and co-stimulatory CD28 molecule on the T-cell membrane. Abatacept intensifies what is a natural counter-regulatory mechanism and appears to have a good safety profile. It has demonstrated efficacy in several chronic inflammatory diseases and is presently approved for the treatment of rheumatoid arthritis resistant to TNF blockade (41, 42). Abatacept is currently being tested in clinical trials for Wegener's granulomatosis, giant-cell arteritis, and Takayasu's disease (www.clinicaltrials.gov).

2.1.6 Hindering Th1 effector functions

It is currently assumed that GCA is a Th1 mediated disease. This concept is supported by the granulomatous nature of the disease suggesting a delayed-type hypersensitivity reaction and by the prominent expression of Th1 cytokines (IFNγ and IL-2), as opposed to the scarce presence of Th2 cytokines in lesions (43). Moreover, expression of IFNγ-induced products such as MHC class II molecules, chemokine receptor CCR2 and receptors for IFNγ-induced chemokines in GCA lesions, further supports this view (22, 33, 44). IFNγ is a potent stimulator of macrophages, which have pivotal effector functions in GCA, and has been considered as a potential target (20). Interestingly, aspirin down-regulates IFNγ expression in human temporal arteries engrafted onto SCID mice (45). Unfortunately, the aspirin doses required to down-regulate IFNγ in this model may be unsafe for human use (45).

A neutralizing humanised monoclonal antibody against IFNγ, fontolizumab, has been tested in other diseases where IFNγ is thought to play a role. Blocking IFNγ has shown moderate efficacy in Crohn's disease but no clear effectiveness in rheumatoid arthritis (46, 47). In addition, two points deserve consideration. Knocking out IFNγ, IFNγ receptor, or IFNγ-related signalling molecules results in severe forms of necrotising vasculitis in mice infected with murine gamma herpes virus 68, indicating that, in this model, the granulomatous reaction or other functions induced by IFNγ might have a limiting effect on destructive, necrotising inflammation (25). Although there is no proof of the participation of latent viruses or other infectious agents in the pathogenesis of GCA, these findings deserve attention. Furthermore, IFNγ deficient mice develop more severe forms of aortic aneurysm induced by aortic allograft transplantation (48). As already mentioned, aortic aneurysm is a significant complication of patients with GCA (12, 14). These observations indicate that a better knowledge of the role of IFNγ in GCA is needed before it can be considered a suitable target.

2.2 Disrupting vessel wall inflammation

Once triggering mechanisms have been unleashed, inflammatory cells including those specifically addressed to the offending trigger, as well as cooperative bystanders, are actively recruited into the vessel wall. Chemokines, adhesion molecules, and proteases are crucial in this process.

2.2.1 Chemokines and chemokine receptors

The influx of leukocytes, mainly $CD4^+$ T lymphocytes and monocytes in GCA is achieved through the secretion of chemoattractants in vascular lesions. Several chemokines are known to be expressed in GCA. Expression of CCL19, and CCL21 chemokines by activated dendritic cells may be a relevant autocrine/paracrine early step, retaining CCR7 bearing dendritic cells in the artery wall, chemoattracting particular T lymphocyte subsets (49), and allowing subsequent antigen presentation to T cells (29). Subsequent recruitment of Th1 lymphocytes and macrophages, the main infiltrating cells in GCA, may be achieved through production of additional chemokines. CCL2/MCP-1 is produced not only by inflammatory cells but also by vascular smooth muscle cells and is a key chemokine in vascular inflammation (33) (Fig. 2). CCL2 is a chemoattractant for Th1 lymphocytes and monocytes, the major components of GCA lesions and may be relevant in the early development of GCA inflammatory infiltrates. Infiltrating leukocytes express, indeed CCR2 receptors, indicating their ability to be chemoattracted by CCL2 (33). Activated tissue macrophages strongly produce CCL2, which may amplify the recruitment of additional monocytes in a positive feed-back loop (Fig. 2). Infiltrating cells in GCA also express CCR5 and CXCR3, chemokine receptors conferring responsiveness to CCL5/RANTES and to CXCL9 (MIG), CXCL10 (IP10), and CXCL11 (ITAC), respectively (44). Interestingly, CCR2 and chemokine ligands of CXCR3, such as CXCL9, CXCL10, and CXCL11, are all induced by IFNγ (50). Therefore, the expression of these chemokines and receptors not

only suggests their participation in the recruitment of inflammatory cells but is in accordance with the observed production of IFNγ in lesions and supports the participation of Th1 mechanisms in GCA.

CCL2/MCP1, the CCR2 ligand, is up-regulated in relapsing, corticosteroid resistant patients with GCA and increased CCL2/MCP-1 expression in lesions at diagnosis is associated with subsequent relapses and higher corticosteroid requirements (33).

Orally administered small molecules able to block chemokine receptors have been developed. This approach has been widely investigated in the human immunodeficiency virus (HIV) field, given that CCR5 is a co-receptor for HIV (51). Blocking chemokines and chemokine receptors in inflammatory conditions faces the challenge of the remarkable redundancy and promiscuity existing among chemokine and chemokine receptors. Compounds able to simultaneously blocking CCR2, CCR5, and CXCR3 have been synthesized and might be useful to treat Th1-mediated chronic inflammatory disases (52). Chemokine receptor antagonists are currently being tested in clinical trials for a variety of conditions (www. clinicaltrials.gov).

2.2.2 Leukocyte/endothelial cell adhesion molecules

Circulating leukocytes infiltrate the artery wall through complex interactions with endothelial cells of adventitial *vasa vasorum* and inflammation-induced neovessels, and the underlying matrix. These interactions are mediated by adhesion molecules. Among them, leukocyte integrins are pivotal in mediating firm adhesion to endothelial cells, transmigration, and progression through the basement membrane and underlying tissue (53, 54).

α4 is the common α chain of integrins α4β1 (VLA4) and α4β7. It is mainly expressed by lymphocytes, eosinophils and monocytes and is crucial for leukocyte infiltration of tissues. VLA-4 serves as a co-stimulatory molecule by interacting with VCAM-1 on antigen-presenting cells and binds VCAM-1, induced on endothelial cells by pro-inflammatory cytokines (53-55). Through a different domain, VLA4 is also able to interact with the extracellular matrix protein fibronectin (53-55). In accord with its crucial role in leukocyte transmigration,VLA 4 is up-regulated in lymphocytes migrating into specific compartments (56, 57). Interestingly, VLA4 engagement by fibronectin triggers matrix metalloproteinase (MMP)-2 and MMP9 production and release by lymphocytes favouring lymphocyte progression through the basement membrane and underlying matrix (58, 59).

VLA4 is strongly expressed by infiltrating lymphocytes in GCA lesions and co-localizes with VCAM-1 on endothelial cells from *vasa vasorum* or inflammation-induced neovessels, suggesting that this interaction may be relevant to the development of vascular inflammation in GCA (60). Moreover, VLA4 co-localizes with MMP2 and MMP9 expression and enzymatic activity, suggesting that VLA-4 blocking may also limit vessel wall destruction (61). Blocking α4 might then act at several levels in GCA immunopathogenesis. Neutralizing α4 integrin with monoclonal antibodies reduces, indeed, severity in animal models of chronic inflammatory diseases including arthritis and experimental allergic encephalitis (57). Natalizumab a humanized neutralizing monoclonal antibody anti-human α4 has demonstrated a remarkable efficacy in Crohn's disease and multiple sclerosis (62, 63). Small inhibitory molecules are also being developed to block α4-mediated interactions (64). The report of some cases of progressive multifocal encephalopathy (PML) in patients treated with natalizumab and interferon alpha has lead to restrictions in its use (65). Until the risk of natalizumab in increasing the frequency of PML is better clarified, trials with this agent may be considered excessively aggressive for patients with GCA.

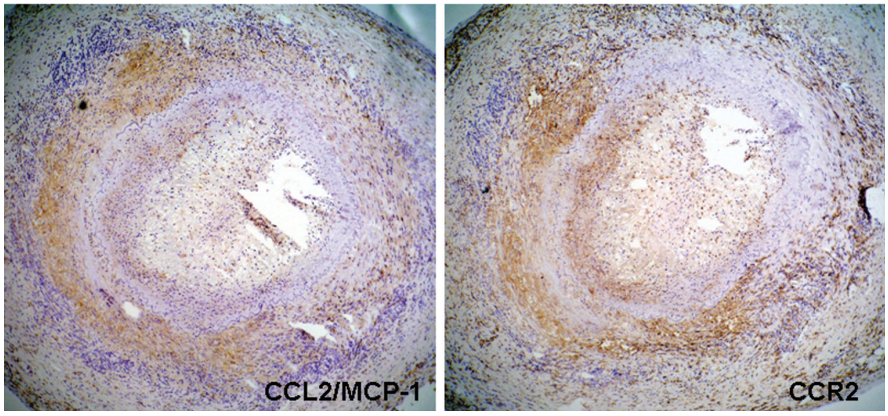

Fig. 2. Temporal artery sections from a patient with giant-cell arteritis (GCA) displaying CCL2/MCP-1 expression by vascular smooth muscle cells and by infiltrating leukocytes, particularly at the granulomatous area. A subset of infiltrating leukocytes expresses CCR2 receptors, suggesting that this and other chemokine/chemokine receptor interactions contribute to vascular inflammation in GCA. Immunostaining of temporal artery sections was performed as described in ref. 33.

colore

2.2.3. Interfering with proinflammatory cascades

i. *Blocking pro-inflammatory cytokines*

A variety of pro-inflammatory cytokines able to maintain and amplify inflammatory cascades are abundantly produced by activated lymphocytes and macrophages in GCA. These include TNF-α, IL1β, and IL-6, among others. These cytokines have potent local and systemic effects: they are powerful inducers of the acute phase response which is prominent in GCA and have profound effects on inflammatory cells and on vascular wall components creating complex interactions and leading to multiple amplification cascades (19, 66) (Fig. 3).

TNF-α is able to maintain inflammatory pathways by promoting the expression of other pro-inflammatory cytokines such as IL-1 and IL-6, by inducing or up-regulating endothelial adhesion molecules for leukocytes such as E-selectin, ICAM-1 and VCAM-1, chemokines such as IL-8 and CCL2/MCP-1,

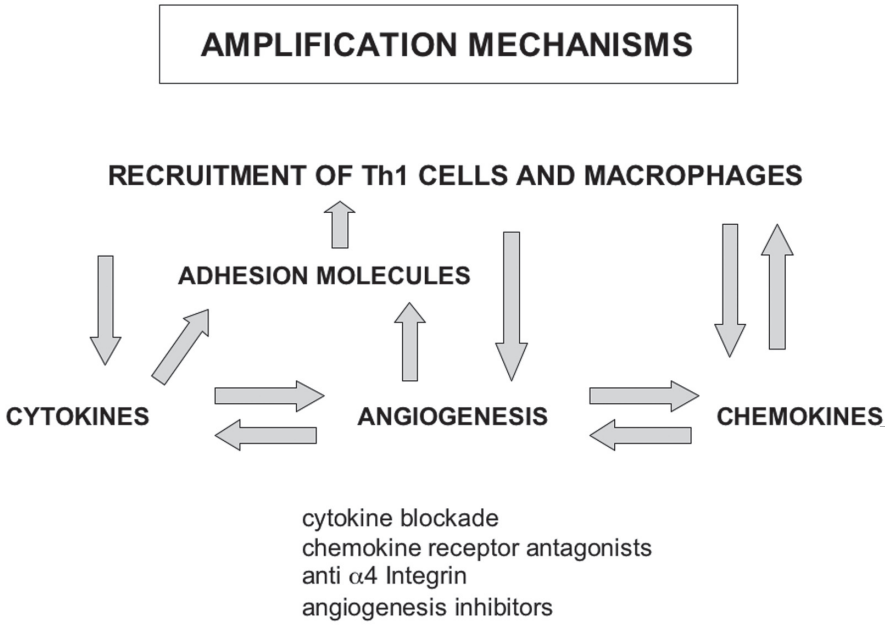

Fig. 3. Diagram disclosing amplification cascades thought to contribute to vascular inflammation in giant-cell arteritis with potential therapeutic targets.

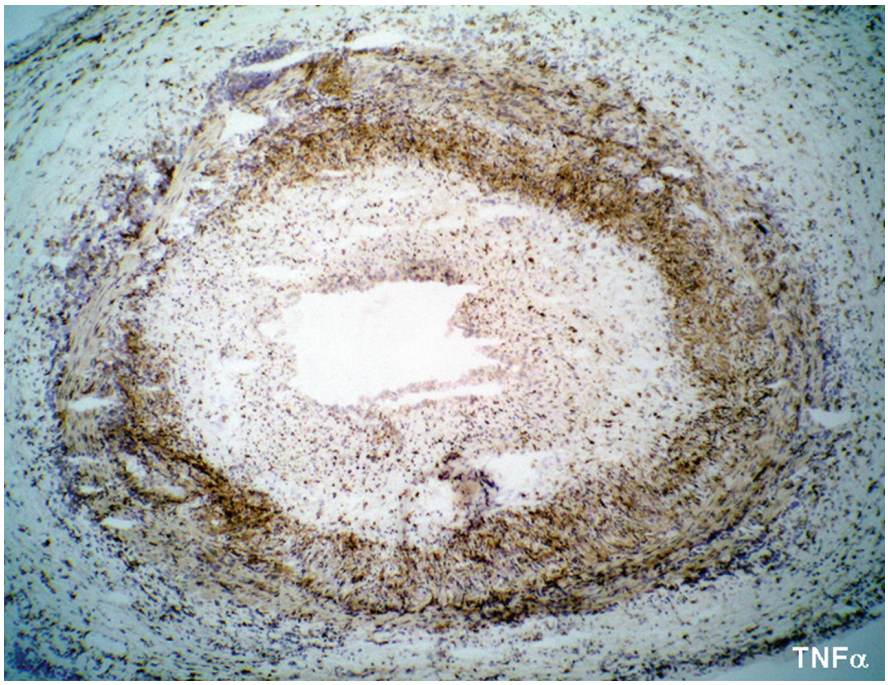

Fig. 4. TNF-α expression is remarkable in giant-cell arteritis, particularly at the granulomatous area, but TNF-α blockade is not sufficient to abrogate disease activity in newly diagnosed patients. Immunostaining of temporal artery sections was performed as described in ref. 67.

matrix metalloproteinases including MMP-1 and MMP-3, and angiogenic factors and receptors, including VEGF and Tie-1 (67). TNF is strongly expressed in GCA lesions and its expression correlates with the systemic inflammatory response and corticosteroid requirements (68) (Fig. 4). Serum TNF-α concentration is increased in patients with strong acute phase reaction who are more resistant to treatment (69) and circulating TNF-α persists elevated in relapsing patients after long-term follow up (70). Furthermore, blocking TNF has demonstrated efficacy in a variety of granulomatous and chronic inflammatory diseases (67) and a small open-label series suggests usefulness in resistant Takayasu's arteritis, a disease sharing many features with GCA (71). While several case reports and small series of patients with refractory GCA responding to TNF blockade have been published, a recent randomized clinical trial failed to demonstrate benefit of infliximab in maintaining remission in newly diagnosed patients with GCA (4). Although this trial does not completely preclude efficacy in sparing glucocorticoids later in the course of the disease, it does indicate that blocking TNF-α is not sufficient to maintain remission achieved with high-dose glucocorticoids in full-blown GCA. Preliminary results from another recent trial suggest that etanercept might have some usefulness in maintaining remission and sparing glucocorticoids in resistant GCA patients or in patients with corticosteroid-related side effects. Unfortunately the number of patients included in this randomized trial was too small to draw solid conclusions (72).

IL-1 shares multiple pro-inflammatory functions with TNF-α. It is also a co-stimulatory cytokine produced by antigen-presenting cells and participates in T cell activation. In addition it is strongly expressed in GCA lesions, particularly in patients with strong systemic inflammatory response which are more refractory to treatment (68). Targeting IL-1 has been found to be effective in autoinflammatory syndromes, diseases caused by mutations in genes encoding proteins participating in innate immune responses (73). IL-1 receptor antagonist (IL-1ra)-deficient mice spontaneously develop large vessel vasculitis (74) with immunopathologic features of a Th1-mediated process (75). Currently, IL-1 biologic activity can be neutralized by recombinant IL-1ra humanized monoclonal antibodies against IL-1β and with an IL-1 trap. At present, there is no experience with IL-1 blockade in GCA.

IL-6 is remarkably produced in GCA lesions and is characteristically elevated in serum form patients with GCA (69, 70, 76). IL-6 serum concentration is more elevated in patients with strong systemic inflammatory response who are more resistant to treatment and persists elevated in relapsing patients after long-term follow-up (69, 70). IL-6 is

colore

a powerful inducer of the systemic inflammatory response. It also contributes to the anemia of chronic disease type by enhancing the hepatic synthesis of hepcidin. IL-6 is a multifunctional cytokine and has additional immunomodulatory effects which may be relevant in the pathogenesis of chronic inflammatory diseases, including B cell activation and induction of Th17 functional differentiation which is a relevant pro-inflammatory pathway promoting autoimmunity (77). Although the participation of B cells and Th17 mechanisms have not been explored in GCA, IL-6 has been considered a potential target in GCA, based on its systemic effects (20). Blocking IL-6 membrane bound and soluble receptors with tocilizumab has shown efficacy in diseases where IL-6 is thought to play a pathogenic role such as Castleman disease, rheumatoid arthritis and systemic-onset juvenile arthritis (77). Interestingly, a recent case report describes improvement in a patient with Takayasu's disease treated with tocilizumab (78). However, several points deserve consideration. Although IL-6 is known to be produced in GCA, the expression of its soluble receptor, which mediates biologic effects in the majority of cells, has not been explored in GCA. Moreover, IL-6 may have a physiologic role in the normal homeostasis of the vascular system since it is substantially expressed in normal temporal arteries (68, 79). Furthermore, IL-6 mRNA and protein expression in lesions as well as IL-6 serum concentrations are negatively associated with the development of GCA-related cranial ischemic complications (80). Although these observations do not definitively demonstrate that IL-6 has a protective function against vascular occlusion, they do suggest caution in blocking IL-6 activity at least in the early treatment of the disease.

ii. Angiogenesis modulation

Angiogenesis results from a delicate balance between angiogenesis stimulators and angiogenesis inhibitors. Neovascularization is a remarkable finding in GCA lesions (81, 82) and various angiogenic (*i.e.*,VEGF, FGF-2, IL-6, IL-8, CCL-2, PDGF, angiogenin) and anti-angiogenic factors (*i.e.*, IFNγ, IP-10) have been demonstrated to be expressed in GCA (20, 33, 66, 79, 83, 84). Angiogenesis is prominent in many chronic inflammatory diseases and has relevant pro-inflammatory functions (66). Neovessels intensively express adhesion molecules for leukocytes providing new sites through which additional leukocytes may be recruited into the inflamed tissues. Moreover, newly formed vessels provide a wide activated endothelial surface, source of cytokines, chemokines and growth factors able to amplify and perpetuate the inflammatory process (66). Angiogenesis inhibitors indeed have ameliorated disease in animal models of chronic rheumatoid arthritis and other chronic inflammatory diseases (85). Efficient therapies for chronic arthritis such as infliximab include, among their effects, angiogenesis inhibition (86).

Several strategies addressed to inhibit angiogenesis have been developed, many of them aimed to neutralize VEGF biologic activity. These include a humanized anti-VEGF (cetuximab) a VEGF trap (aflibercept) and inhibitors of the tyrosine kinase activity of VEGF receptor (semaxanib). These are currently in clinical trials, mainly in the oncology field (www.clinicaltrials.gov). Targeting angiogenesis in GCA requires a better understanding of the functional relevance of the factors known to be expressed in lesions. Moreover, vasculitis are unique among chronic inflammatory diseases given that the inflammatory process leads eventually to blood vessel occlusion and angiogenesis may compensate for ischemia. In GCA, an intense angiogenic response in lesions and angiogenic activity in serum is associated with lower frequency of disease-related cranial ischemic complications (81). Although GCA is considered a large and medium size vessel vasculitis, small cranial vessels and small arteries supplying the optic nerve are frequently involved and neovascularisation may compensate for ischemia at distal sites (88, 89). Supporting this concept, certain polymorphisms at the VEGF gene are associated with higher frequency of disease-related ischemic complications. (89) Targeting angiogenesis may then be harmful, at least in certain patients or at certain disease stages. A better understanding of the role of angiogenesis in GCA is needed before angiogenesis inhibition or promotion is considered as a therapeutic target.

3. Avoiding vascular destruction

Inflammatory infiltration of the vessel wall disrupts its normal architecture (Fig. 5). In GCA, the internal elastic lamina appears typically fragmented. Disruption of elastic fibers in the aortic wall may lead over time to the development of aortic dilatation or aneurysm with the potential of severe complications (90). Several enzymes with elastinolytic capability are expressed in GCA lesions. These include MMP9, MMP2, and MMP12 (91, 92). All these are present in their active form and are intensively expressed around the internal elastic lamina where enzymatic activity is also maximal (91, 92). In addition to their destructive potential, MMPs have a complex role in inflammation. They promote inflammation, by allowing the progression of inflammatory cells through the artery wall (61, 91, 93). MMPs also regulate the inflammatory process by activating cytokines and chemokines by proteolytic cleavage and by exposing bioactive cryptic sites in large extracellular matrix proteins and these may include some anti-inflammatory functions (93). Illustrating this point, mice deficient in MMP2 develop more severe forms of collagen induced arthritis and EAE (Experimental Allergic Encephalitis), underlining the intricacy of MMP functions in inflammatory diseases (94). Adding complexity, MMP may have a dual function in vascular remodelling: by disrupting IEL they may promote myointimal cell migration but, at the same time, increased MMP expression and activity may prevent excessive matrix deposition and lumen occlusion (95). The therapeutic use of MMP inhibitors (*i.e.*, marimastat) has been addressed in oncology although results are less impressive than initially expected (93). They are currently being tested as part of combined therapies (www.clinicaltrials.gov). Given the complex functions of MMPs, their role in GCA needs to be investigated in more depth before MMP

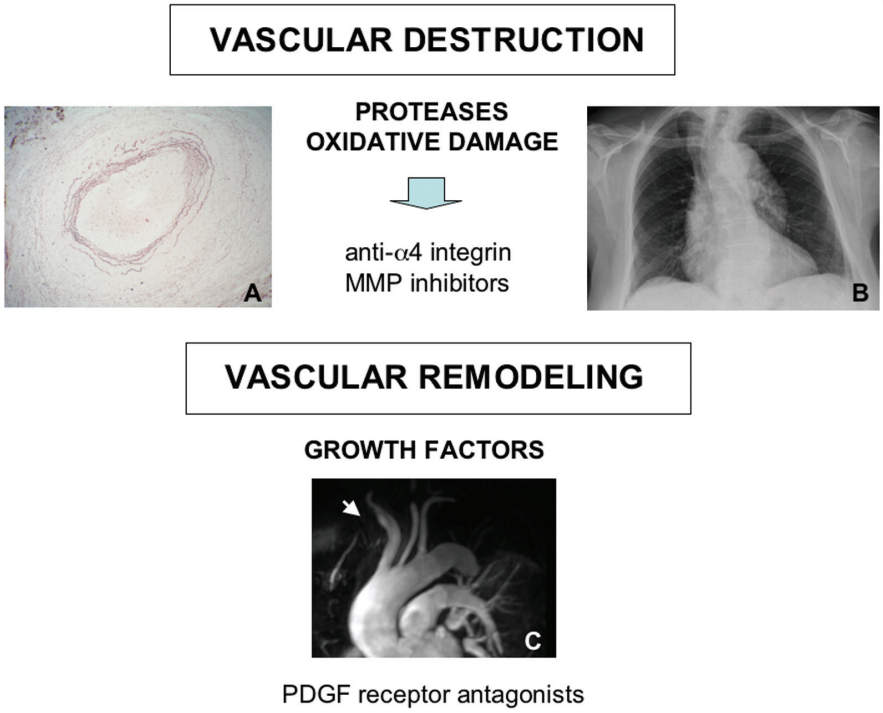

Fig. 5. Mechanisms of vascular destruction and remodelling in giant-cell arteritis and potential therapeutic intervention. **A**) Disruption of the internal elastic lamina, as evidenced by orcein staining. **B**) Aortic aneurysm as a delayed consequence of vascular destruction. **C**) Subclavian stenosis (arrow).

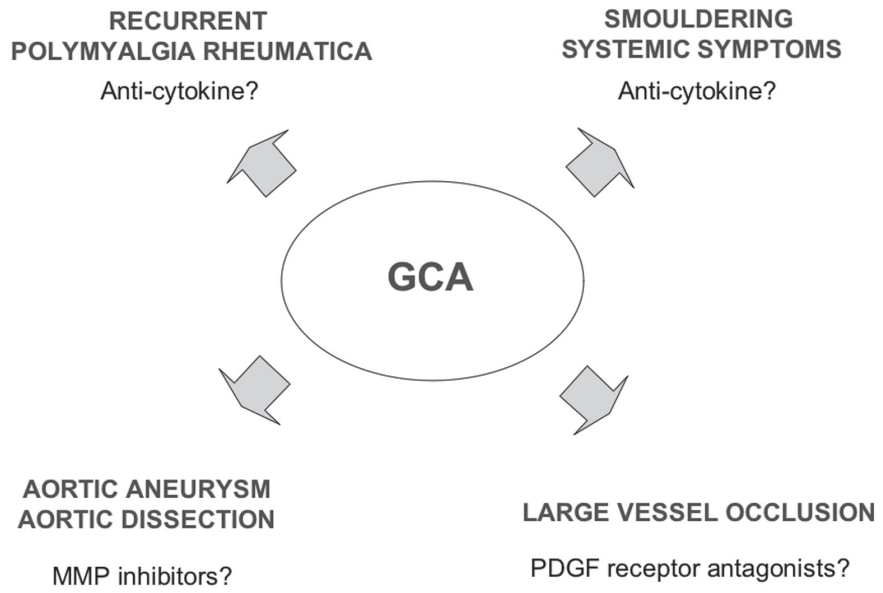

Fig. 6. Different challenges in the outcome of patients with GCA that may need to be specifically addressed with targeted therapies.

inhibitors are considered as therapeutic tools to limit vascular wall destruction in GCA. The effects of commonly used drugs which include, among other effects, some MMP inhibition such as statins or doxycycline are currently being tested in the medical management of small abdominal aneurysms complicating other conditions (96, 97). Interestingly, in a recent study, the development of aortic aneurysm in the long-term follow-up of GCA was significantly less frequent in patients receiving statins for hypercholesterolemia (12).

4. Limiting vascular occlusion

Intimal hyperplasia is the result of inflammation-induced vessel remodelling and the main mechanism leading to vascular occlusion and ischemic complications in GCA (19, 20, 84) (Fig. 5C). During active disease, occlusive phenomena are more frequent in cranial arteries but may also occur in the aortic branches leading to limb claudication (13, 14). Occasionally, stenosis of other vascular beds may lead to coronary events or mesenteric ischemia (98).

Upon injury, vascular smooth muscle cells evolve from their quiescent contractile status and acquire a myointimal phenotype resulting in proliferation, migration towards the lumen and production of matrix proteins. Several mesenchymal growth factors able to stimulate proliferation of myointimal cells are known to be expressed in temporal artery biopsies from patients with GCA. These include PDGF, IL-1β, FGF-2, EGF among others (33, 43, 83, 84). Among them, PDGF is the most active in stimulating proliferation and migration of temporal artery derived myointimal cells. PDGF increases the production of matrix proteins and also pro-inflammatory and angiogenic molecules such as CCL-2, and angiogenin (84). These effects of PDGF are abrogated by the tyrosine kinase inhibitor imatinib mesylate which is also able to reduce, but not abrogate, myointimal cell outgrowth from cultured human temporal artery explants from patients with GCA (84). This observation is important since a certain extent of intimal hyperplasia may be necessary to reinforce an injured vascular wall in order to prevent dilatation and rupture. Imatinib mesylate has a favourable safety profile (99) and might be considered to limit vascular stenosis in patients with large vessel vasculitis.

5. Concluding remarks

A wide array of potential new therapies is emerging as the understanding of the molecular mechanisms involved in chronic inflammatory diseases makes progress. New therapies aimed to target specific mechanisms are appealing but it must be kept in mind that our current understanding of the pathogenic mechanisms involved in GCA relies mainly on observational studies with low level of experimental evidence. Current *ex vivo* models (engrafting onto SCID

mice or culture of arterial explants) (45, 79, 100) are useful tools to evaluate molecular changes after therapeutic manipulation but the lack of true animal models prevents the assessment of the impact of therapeutic intervention on disease outcome beyond analysis of biomarker modification. The validity of the proposed therapeutic targets can only be confirmed with clinical trials, underlining the need of multicenter and international collaboration.

It is also important to note that the unresolved challenges that GCA poses to affected individuals are heterogeneous: some patients suffer from the consequences of vascular occlusion, other patients are mainly afflicted by excessive vascular destruction leading to aneurysm or dissection, and in other patients quality of life is impaired by systemic smouldering activity (anemia, malaise, low grade fever, anorexia), recurrent polymyalgia rheumatica or iatrogenic complications (Fig. 6). These disease consequences may need to be approached differently, indicating that tailored or combined therapies addressing specific points may need to be considered. Finally, although all the many potential points of intervention must be considered, it must not be forgotten that a non-negligible proportion of patients do reasonably well with glucocorticoid therapy (1, 101-103). This fact raises concerns about indiscriminately subjecting newly diagnosed patients with GCA to potentially harmful new agents.

References

1. SALVARANI C, CANTINI F, BOIARDI L, HUNDER GG: Polymyalgia rheumatica and giant-cell arteritis. *N Engl J Med* 2002; 347: 261-71.
2. CID MC, GARCÍA-MARTÍNEZ A, LOZANO E, ESPÍGOL-FRIGOLÉ G, HERNÁNDEZ-RODRÍGUEZ J: Five clinical conundrums in the management of giant cell arteritis. *Rheum Dis Clin North Am* 2007; 33: 819-34.
3. HOFFMAN GS, CID MC, HELLMANN DB *et al*.: A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant-cell arteritis. *Arthritis Rheum* 2002; 46: 1309-18.
4. HOFFMAN GS, CID MC, RENDT-ZAGAR KE *et al*.: Infliximab for maintenance of glucocorticosteroid-induced remission of giant-cell arteritis. *Ann Intern Med* 2007; 146: 621-30.
5. CID MC, FONT C, ORISTRELL J *et al*.: Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. *Arthritis Rheum* 1998; 41: 26-32.
6. GONZÁLEZ-GAY MA, GARCÍA-PORRUA C, LLORCA J *et al*.: Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. *Medicine* (Baltimore) 2000; 79: 283-92.
7. NESHER G, BERKUN Y, MATES M *et al*.: Risk factors for cranial ischemic complications in gaint-cell arteritis. *Medicine* (Baltimore) 2004; 83: 114-22.
8. FOROOZAN R, DERAMO VA, BUONO LM *et al*.: Recovery of visual function in patients with biopsy-proven giant-cell arteritis. *Ophthalmology* 2003; 110: 539-42.
9. HAYREH SS, ZIMMERMAN B, KARDON RH *et al*.: Visual improvement with corticosteroid therapy in gaint-cell arteritis. Report of a large study and review of literature. *Acta Ophthalmol Scand* 2002; 80: 353-67.
10. HAYREH SS, ZIMMERMAN B: Visual deterioration in giant-cell arteritis patients while on high doses of corticosteroid therapy. *Ophthalmology* 2003; 110: 1204-15.
11. LIU GT, GLASER JS, SCHATZ NJ *et al*.: Visual morbidity in giant-cell arteritis. Clinical characteristics and prognosis for vision. *Ophthalmology* 1994; 101: 1779-85.
12. GARCÍA-MARTÍNEZ A, HERNÁNDEZ-RODRÍGUEZ J, ARGUIS P *et al*.: Development of aortic aneurysm/dilatation during the follow up of patients with giant cell arteritis: a cross-sectional screening of fifty-four prospectively followed patients. *Arthritis Rheum* 2008; 59: 422-30.
13. KLEIN RG, HUNDER GG, STANSON AW *et al*.: Large artery involvement in giant-cell (temporal) arteritis. *Ann Intern Med* 1975; 83: 806-12.
14. NUENNINGHOFF DM, HUNDER GG, CHRISTIANSON TJH *et al*.: Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis. A population-based study over 50 years. *Arthritis Rheum* 2003; 48: 3522-31.
15. WILKE WS, HOFFMAN GS: Treatment of corticosteroid-resistant giant-cell arteritis. *Rheum Clin Dis North Am* 1995; 21: 59-71.
16. PROVEN A, GABRIEL S, ORCES C, O'FALLON M, HUNDER GG: Glucocorticoid therapy in giant-cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003; 49: 703-8.
17. DELECOEUILLERIE G, JOLY P, COHEN DE LARA A, PAOLAGGI JB: Polymyalgia rheumatica and temporal arteritis: a retrospective analysis of prognostic features and different corticosteroid regimens (11 year survey of 210 patients) *Ann Rheum Dis* 1988; 47: 733: 9.
18. ANDERSSON R, MALMVALL BE, BENGTSSON BA: Long-term corticosteroid treatment in giant-cell arteritis. *Acta Med Scand* 1986; 220: 465-9.
19. CID MC, FONT C, COLL-VINENT B, GRAU JM: Large vessel vasculitides. *Curr Opin Rheumatol* 1998; 10: 18-28.
20. WEYAND CM, GORONZY JJ: Medium- and large-vessel vasculitis. *N Engl J Med* 2003; 349: 160-9.
21. HERNÁNDEZ-RODRÍGUEZ J, FONT C, GARCÍA-MARTÍNEZ A *et al*.: Development of ischemic complications in patients with giant cell arteritis presenting with apparently isolated polymyalgia rheumatica: study of a series of 100 patients. *Medicine* (Baltimore) 2007; 86: 233-41.
22. CID MC, CAMPO E, ERCILLA MG *et al*.: Immunohistochemical analysis of lymphoid and macrophage cell subsets and their immunological activation markers in temporal arteritis. Influence of corticosteroid treatment. *Arthritis Rheum* 1989; 32: 884-93.
23. MA-KRUPA W, JEON MS, SPOERL S, TEDDER TF, GORONZY JJ, WEYAND CM: Activation of arterial wall dendritic cells and breakdown of self-tolerance in giant cell arteritis. *J Exp Med* 2004; 199: 173-83.
24. WEYAND CM, SCHÖNBERGER J, OPPITZ U, HUNDER NN, HICOK KC, GORONZY JJ: Distinct vascular lesions in giant cell arteritis share identical T cell clonotypes. *J Exp Med* 1994; 179: 951-60.
25. WECK KE, DAL CANTO AJ, GOUD JD *et al*.: Murine gammaherpes virus 68 causes large vessel arteritis in mice lacking interferon-gamma responsiveness: a new model from virus-induced vascular disease. *Nat Med* 1997; 3: 1346-53.
26. RODRÍGUEZ-PLA A, BOSCH GIL JA, ECHEVARRIA-MAYO JE *et al*.: No detection of parvovirus B19 or herpesvirus DNA in giant cell arteritis. *J Clin Virol* 2004; 31: 11-5.
27. ALVAREZ-LAFUENTE A, FERNANDEZ-GUTIERREZ B, JOVER JA *et al*.: Human parvovirus B19, varicella zoster virus, and human herpes virus 6 in temporal artery biopsy specimens of patients with giant cell arteritis: analysis with quantitative real time polymerase chain reaction. *Ann Rheum Dis* 2005; 64: 780-2.
28. HELWEG-LARSEN J, TARP B, OBEL N, BASLUND B: No evidence of parvovirus B19, Chlamydia pneumoniae or human herpes virus infection in temporal artery biopsies in patients with giant cell arteritis. *Rheumatology* (Oxford) 2002; 41: 445-9.
29. MA-KRUPA W, DEWAN M, JEON MS, KURTIN PJ *et al*.: Trapping of misdirected dendritic cells in the granulomatous lesions of giant cell arteritis. *Am J Pathol* 2002; 161: 1815-23.
30. VOGL T, TENBROCK K, LUDWIG S *et al*.: MRP8 and MRP14 are endogenous activators of Toll-like receptor 4, promoting lethal, endotoxin-induced shock. *Nat Med* 2007; 13: 1042-9.
31. FOELL D, HERNÁNDEZ-RODRÍGUEZ J, SÁNCHEZ M, VOGL T,CID MC, ROTH J: Early recruitment of phagocytes contributes to the vascular inflammation of giant cell arteritis. *J Pathol* 2004; 204: 311-6.
32. HAJJ-ALI R, HAMILTON T, LEE M *et al*.: Temporal artery expression profiles may predict conditions necessary for developing giant-cell arteritis. *Arthritis Rheum* 2006; 54 (Suppl.): S756.
33. CID MC, HOFFMAN MP, HERNÁNDEZ-RODRÍGUEZ J *et al*.: Association between increased CCL2 (MCP-1) expression in lesions and persistence of disease activity in giant-cell arteritis. *Rheumatology* (Oxford) 2006; 45: 1356-63.
34. BOSSHART H, HEINZELMANN M: Targeting

bacterial endotoxin: two sides of a coin. *Ann NY Acad Sci* 2007; 1096: 1-17.
35. STOLL LL, DENNING GM, WEINTRAUB NL: Endotoxin, TLR-4 signaling and vascular inflammation. Potential therapeutic targets in cardiovascular disease. *Curr Pharmacol Des* 2006; 12: 4229-45.
36. BRACK A, GEISLER A, MARTÍNEZ-TABOADA VM, YOUNGE BR, GORONZY JJ, WEYAND CM: Giant cell vasculitis is a T cell-dependent disease. *Mol Med* 1997; 3: 530-43.
37. MAGLIOCCA JF, KNECHTLE SJ: The evolving role of alemtuzumab (CAMPATH-1H) for immunosuppressive therapy in organ transplantation. *Transplant Int* 2006; 19: 705-14.
38. WALSH M, CHAUDHRY A, JAYNE DR: Long-term follow-up of relapsing/refractory ANCA associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H). *Ann Rheum Dis* 2007 Nov 29. [Epub ahead of print].
39. MARTÍNEZ-TABOADA VM, BRACK A, HUNDER GG, GORONZY JJ, WEYAND CM: The inflammatory infiltrate in giant cell arteritis selects against B lymphocytes. *J Rheumatol* 1996; 23: 1011-4.
40. BHATIA A, ELL PJ, EDWARDS JC: Anti-CD20 monoclonal antibody (rituximab) as an adjunct in the treatment of giant cell arteritis. *Ann Rheum Dis* 2005; 64: 1099-100.
41. KREMER JM, GENANT HK, MORELAND LW: Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006; 144: 865-76
42. SALLIOT C, DOUGADOS M, GOSSEC L: Risk of serious infections during rituximab, abatacept and anakinra therapies for rheumatoid arthritis: meta-analyses of randomized placebo-controlled trials. *Ann Rheum Dis* 2008 Jan 18. [Epub ahead of print].
43. WEYAND CM, HICOK KC, HUNDER GG, GORONZY JJ: Tissue cytokine pattern in patients with polymyalgia rheumatica and giant-cell arteritis. *Ann Intern Med* 1994; 121: 484-91.
44. BRÜHL H, VIELHAUER V, WEISS M, MACK H, SCHLÖNDORFF D, SEGERER S: Expression of DARC, CXCR3 and CCR5 in giant cell arteritis. *Rheumatology* (Oxford) 2005; 44: 309-13.
45. WEYAND CM, KAISER M, YANG H, YOUNGE B, GORONZY JJ: Therapeutic effects of acetylsalicylic acid in giant cell arteritis. *Arthritis Rheum* 2002; 46: 457-66.
46. GHOSH S, CHAUDHARY R, CARPANI M, PLAYFORD R: Interfering with interferons in inflammatory bowel diseases. *Gut* 2006; 55: 1071-3.
47. HOMMES DW, MIKHAJLOVA TL, STOINOV S *et al*.: Fontolizumab, a humanised anti-IFNγ antibody demonstrates safety and clinical activity in patients with moderate to severe Crohn's disease. *Gut* 2006; 55: 1131-7.
48. SHIMIZU K, SHICHIRI M, LIBBY P, LEE RT, MITCHELL RN: Th2-predominant inflammation and blockade of IFN-gamma signalling induce aneurysms in allografted aortas. *J Clin Invest* 2004; 114: 300-8.
49. WORBS T, MEMPEL TR, BÖLTER J, VON ADRIAN VH, FOISTER R: CCR7 ligands stimulate the intranodal mobility of T lymphocytes in vivo. *J Exp Med* 2007; 204: 489-95.
50. HU X, PARK-MIN KH, HO HH, IVASHKIV LB: IFNγ primed macrophages exhibit increased CCR2-dependent migration and altered IFNγ responses mediated by Stat1. *J Immunol* 2005; 175: 3637-47.
51. KUHMANN SE, HARTLEY O: Targeting chemokine receptors in HIV: a status report. *Annu Rev Pharmacol Toxicol* 2008; 48: 425-61.
52. VIOLA A, LUSTER AD: Chemokines and their receptors:drug targets in immunity and inflammation. *Annu Rev Pharmacol Toxicol* 2008; 48: 171-97.
53. CID MC, BIELSA I, COLL-VINENT B: Endothelial cell adhesion molecules. *In* Inflammatory diseases of blood vessels. Ed. GS Hoffman and CM Weyand. 2001. Marcel Dekker, Inc. New York-Basel. pp 13-28.
54. CID MC, VILARDELL C: Tissue targeting and disease patterns in systemic vasculitis. *Best Pract Res Clin Rheumatol* 2001: 259-79.
55. LEY K, LAUDANNA C, CYBULSKI MI, NOURSHARGH S: Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nat Rev Immunol* 2007; 7: 678-89.
56. LAFFON A, GARCÍA-VICUÑA R: Humbría A *et al*.: Upregulated expression and function of VLA-4 fibronectin receptors on human activated T cells in rheumatoid arthritis. *J Clin Invest* 1991; 88: 546-52.
57. YEDNOCK TA, CANNONC, FRITZ LC, SÁNCHEZ-MADRID F, STEINMAN L, KARIN N: Prevention of experimental autoimmune encephalomyelitis by antibodies against alpha 4 beta 1 integrin. *Nature* 1992; 356: 63-6.
58. ESPARZA J, VILARDELL C, CALVO J *et al*.: Fibronectin up-regulates gelatinase B (MMP-9) and induces coordinated expression of gelatinase A (MMP-2) and its activator MT1-MMP (MMP-14) by human T lymphocyte cell lines. A process repressed through RAS/MAP kinase signaling pathways. *Blood* 1999; 94: 2754-66.
59. SEGARRA M, VILARDELL C, MATSUMOTO K *et al*.: Dual function of focal adhesión kinase in regulating integrin-induced MMP2 and MMP9 release by human T lymphoid cell lines. *FASEB J* 2005; 19: 1875-7.
60. CID MC, CEBRIÁN M, FONT C *et al*.: Cell adhesion molecules in the development of inflammatory infiltrates in giant-cell arteritis. Inflammation-induced angiogenesis as the preferential site of leukocyte-endothelial cell interactions. *Arthritis Rheum* 2000; 43: 184-94.
61. SEGARRA M, GARCÍA-MARTÍNEZ A, SÁNCHEZ M *et al*.: Leukocyte integrin alpha 4 is associated with gelatinase (MMP2 and MMP9) and MMP14 expression and activation in GCA lesions. *Arthritis Rheum* 2006; 54 (Suppl): S578-9.
62. SANDBORN WJ: Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2005; 353: 1912-25.
63. POLMAN CH, O'CONNOR PW, HAVRDOVA E *et al*.: A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; 354: 899-910.
64. CORTIJO J, SANZ MJ, IRANZO A *et al*.: A small molecule, orally active, alpha4beta1/alpha4beta7 dual antagonist reduces leukocyte infiltration and airway hyper-responsiveness in an experimental model of allergic asthma in Brown Norway rats. *Br J Pharmacol* 2006; 147: 661-70.
65. BERGER JR: Natalizumab and progressive multifocal leucoencephalopathy. Ann Rheum Dis 2006; 65 (Suppl. 3): III48-53.
66. CID MC: Endothelial cell biology, perivascular inflammation, and vasculitis. *Cleve J Med* 2002; 62 (Suppl. 2): 45-50.
67. FELDMANN M, MAINI RN: Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? *Annu Rev Immunol* 2001; 19: 163-96.
68. HERNÁNDEZ-RODRÍGUEZ J, SEGARRA M, VILARDELL C *et al*.: Tissue production of pro-inflammatory cytokines (IL-1beta, TNF-alpha and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. *Rheumatology* (Oxford) 2004; 43: 294-301.
69. HERNÁNDEZ-RODRÍGUEZ J, GARCÍA-MARTÍNEZ A, CASADEMONT J *et al*.: A strong initial systemic inflammatory response is associated with higher corticosteroid requirements and longer duration of therapy in patients with giant-cell arteritis. *Arthritis Rheum* 2002; 47: 29-35.
70. GARCÍA-MARTÍNEZ A, HERNÁNDEZ-RODRÍGUEZ J, SEGARRA M *et al*.: Clinical relevance of persistenly elevated circulating cytokines (TNFα and IL-6) in the long-term follow-up of patients with giant-cell arteritis (GCA). *Arthritis Rheum* 2006; 54: S763.
71. HOFFMAN GS, MERKEL PA, BRASSINGTON RD, LENSCHOW DJ, LIANG P: Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum* 2004; 50: 2296-304.
72. MARTÍNEZ-TABOADA VM, RODRÍGUEZ-VALVERDE V, CARREÑO L *et al*.: A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. *Ann Rheum Dis* 2008; 67: 625-30.
73. CHURCH LD, CHURCHMAN SM, HAWKINS PN, MCDERMOTT MF: Hereditary auto-inflammatory disorders and biologics. S*pringer Semin Immunopathol* 2006; 27: 494-508.
74. NICKLIN MJ, HUGHES DE, BARTON JL, URE JM, DUFF GW: Arterial inflammation in mice lacking the interleukin 1 receptor antagonist gene. *J Exp Med* 2000; 191: 303-12.
75. SHEPHERD J, NICKLIN MJ: Elastic-vessel arteritis in interleukin-1 receptor antagonist-deficient mice involves effector Th1 cells and requires interleukin-1 receptor. *Circulation* 2005; 111: 3135-40.
76. DASGUPTA B, PANAYI GS: Interleukin-6 in serum of patients with polymyalgia rheumatica and giant cell arteritis. *Br J Rheumatol* 1990; 29: 456-8.
77. OHSUGI Y: Recent advances in immunopathophysiology of interleukin-6: an innovative therapeutic drug, tocilizumab (recombinant humanized anti-human interleukin-6 receptor antibody), unveils the mysterious etiology of immune-mediated inflammatory diseases. *Biol Pharm Bull* 2007; 30: 2001-6.

78. NISHIMOTO N, NAKAHARA H, YOSHIO-HOSHIMO N, MIMA T: Successful treatment of a patient with Takayasu arteritis using a humanized anti-interleukin-6 receptor antibody. *Arthritis Rheum* 2008; 58: 1197-200.
79. GARCÍA-MARTÍNEZ A, LOZANO E, SEGARRA M *et al*.: Human temporal artery culture on Matrigel: a useful method for preclinical assessment of functional changes after intervention. *Arthritis Rheum* 2007; 56 (Suppl.): S497.
80. HERNÁNDEZ-RODRÍGUEZ J, SEGARRA M, VILARDELL C *et al*.: Elevated production of interleukin-6 is associated with a lower incidence of disease-related ischemic events in patients with giant-cell arteritis: angiogenic activity of interleukin-6 as a potential protective mechanism. *Circulation* 2003; 107: 2428-34.
81. CID MC, HERNÁNDEZ-RODRÍGUEZ J, ESTEBAN MJ *et al*.: Tissue and serum angiogenic activity is associated with low prevalence of ischemic complications in patients with giant-cell arteritis. *Circulation* 2002; 106: 1664-71.
82. NORDBORG C,LARSSON K, NORDBORG E: Stereological study of neovascularization in temporal arteritis. *J Rheumatol* 2006; 33: 2020-5.
83. KAISER M, YOUNGE B, BJÖRNSSON J, GORONZY JJ, WEYAND CM: Formation of new vasa vasorum in vasculitis. Production of angiogenic cytokines by multinucleated giant cells. *Am J Pathol* 1999; 155: 765-74.
84. LOZANO E, SEGARRA M, GARCÍA-MARTÍNEZ A, HERNÁNDEZ-RODRÍGUEZ J, CID MC: Imatinib mesylate inhibits in vitro and ex vivo biologic responses related to vascular occlusion in giant-cell arteritis. *Ann Rheum Dis* 2007 Jun 21; [Epub ahead of print].
85. BAINBRIDGE J, SIVAKUMAR B, PALEOLOG E: Angiogenesis as a therapeutic target in arthritis: lessons from oncology. *Curr Pharm Des* 2006; 12: 2631-44.
86. CAÑETE JD, PABLOS JL, SANMARTÍ R *et al*.: Antiangiogenic effects of anti-tumor necrosis factor alpha therapy with infliximab in psoriatic arthritis. *Arthritis Rheum* 2004; 50: 1636-41.
87. ESTEBAN MJ, FONT C, HERNÁNDEZ-RODRÍGUEZ J *et al*.: Small-vessel vasculitis surrounding a spared temporal artery: clinical and pathological findings in a series of twenty-eight patients. *Arthritis Rheum* 2001; 44: 1387-95.
88. GARCÍA-PORRÚA C, PEGO-REINOSA R, ARMESTO V, GONZÁLEZ-GAY MA: Neovascularization around the optic nerve in giant cell arteritis. *Arthritis Rheum* 2003; 49: 737-8.
89. RUEDA B, LÓPEZ-NEVOT MJ, GARCÍA-PORRÚA C, MARTÍN J, GONZÁLEZ-GAY MA: A functional variant of vascular endothelial growth factor is associated with severe ischemic complications in giant cell arteritis. *J Rheumatol* 2005; 32: 1737-41.
90. LIE JT: Aortic and extracranial large vessel giant cell arteritis: a review of 72 cases with histopathologic documentation. *Semin Arthritis Rheum* 1995; 24: 422-31.
91. SEGARRA M, GARCÍA-MARTÍNEZ A, SÁNCHEZ M *et al*.: Gelatinase expression and proteolytic activity in giant-cell arteritis. *Ann Rheum Dis* 2007; 66: 1429-35.
92. SEGARRA M, SÁNCHEZ M, LOZANO E *et al*.: Matrix metalloelastase (MMP12) expresión in giant-cell arteritis lesions. *Ann Rheum Dis* 2007; 66 (Suppl.): S383-4.
93. MANICONE AM, MCGUIRE JK: Matrix metalloproteases as modulators of inflammation. *Semin Cell Dev Biol* 2008; 19: 34-41.
94. ESPARZA J, KRUSE M, LEE J, MICHAUD M, MADRI JA: MMP-2 null mice exhibit an early onset and severe experimental autoimmune encephalomyelitis due to an increase in MMP-9 expression and activity. *FASEB J* 2004; 18: 1682-91.
95. FURMANIAK-KAZMIERCZAK E, CRAWLEY SW, CARTER RL: Formation of extracellular matrix-digesting invadopodia by primary aortic smooth muscle cells. *Circ Res* 2007; 100: 1328-36.
96. CHUNG AW, YANG HH, RADOMSKI MW, VAN BREEMEN C: Long-term doxycycline is more effective than atenolol to prevent thoracic aortic aneurysm in Marfan syndrome through the inhibition of matrix metalloproteinase-2 and -9. *Circ Res* 2008; 102:e 73-85.
97. BAXTER BT, TERRIN MC, DALMAN RL: Medical management of small abdominal aortic aneurysms. *Circulation* 2008; 117: 1883-9.
98. SUJOBERT P, FARDET L, MARIE I *et al*.: Mesenteric ischemia in giant cell arteritis: 6 cases and a systematic review. *J Rheumatol* 2007; 34: 1727-32.
99. DRUKER BJ,GUILHOT F, O'BRIEN SG: Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006; 355: 2408-17.
100. BRACK A, RITTNER HL, YOUNGE BR, KALTSCHMIDT C, WEYAND CM, GORONZY JJ: Glucocorticoid-mediated repression of cytokine gene transcription in human arteritis-SCID chimeras. *J Clin Invest* 1997; 99: 2842-50.
101. WARRINGTON KJ, MATTESON EL: Management guidelines and outcome measures in giant-cell arteritis (GCA). *Clin Exp Rheumatol* 2007; 25 (Suppl. 47): 137-41.
102. DASGUPTA B, HASSAN N: British Society fro Rheumatology guidelines group. Giant cell arteritis: recent advances and guidelines for management. *Clin Exp Rheumatol 2007*; 25 (Suppl. 44): S62-5.
103. MAKSIMOWICZ-MCKINNON K, HOFFMAN GS: Large vessel vasculitis. *Clin Exp Rheumatol* 2007; 25 (Suppl. 44): S58-9.