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REVIEW

What Is the Current Evidence for Disease Subsets in Giant Cell Arteritis?

Kornelis S. M. van der Geest, Maria Sandovici, Yannick van Sleen, Jan-Stephan Sanders, Nicolaas A. Bos, Wayel H. Abdulahad, Coen A. Stegeman, Peter Heeringa, Abraham Rutgers^{id}, Cees G. M. Kallenberg, Annemieke M. H. Boots, and Elisabeth Brouwer

Giant cell arteritis (GCA) is an autoimmune vasculitis affecting large and medium-sized arteries. Ample evidence indicates that GCA is a heterogeneous disease in terms of symptoms, immune pathology, and response to treatment. In the current review, we discuss the evidence for disease subsets in GCA. We describe clinical and immunologic characteristics that may impact the risk of cranial ischemic symptoms, relapse rates, and long-term glucocorticoid requirements in patients with GCA. In addition, we discuss both proven and putative immunologic targets for therapy in patients with GCA who have

an unfavorable prognosis. Finally, we provide recommendations for further research on disease subsets in GCA.

Introduction

Giant cell arteritis (GCA) is the most prevalent form of autoimmune vasculitis in elderly individuals. GCA is characterized by inflammation of medium-sized cranial arteries and large systemic arteries. Cranial ischemic symptoms are well-known complications of GCA and may include sight loss and stroke. In addition, many patients experience symptoms of systemic inflammation, such as fatigue, low-grade fever, and weight loss. Inflammation marker levels are typically elevated in the blood of patients with GCA (1). Glucocorticoids are the cornerstone of treatment. Early initiation of high-dose glucocorticoids led to a substantial decrease in visual symptoms among GCA patients over the last decades (2). However, side effects are frequently encountered with long-term glucocorticoid treatment in elderly patients with GCA (3). Recently, novel targeted treatments have emerged as potent alternatives for maintenance of glucocorticoid-free disease remission in patients with GCA (4–6).

Accumulating evidence indicates that GCA is a heterogeneous disease. The extent of the local and systemic inflammatory response may differ among GCA patients (1). Moreover, distinct immune cells and cytokines may predominate at the site of vascular inflammation in individual patients (7). Various clinical and immunologic factors have been linked to the risk of cranial ischemic symptoms, relapse rates, and overall glucocorticoid requirements in patients with GCA. Immunologic heterogeneity in GCA is further suggested by outcomes of recent trials with anti-interleukin-6 receptor (anti-IL-6R) and CTLA-4Ig

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therapy, because these targeted treatments are not effective in all GCA patients (4–6). Taken together, these findings indicate that there may be distinct categories of GCA patients. Recognition of distinct GCA subsets is important, because it may eventually help to implement precision medicine for GCA.

In this review, we provide an overview of current evidence for disease subsets in GCA. We describe the prognostic relevance of clinical disease characteristics in patients with GCA, i.e., the systemic inflammatory response, coexistent polymyalgia rheumatica (PMR), and involvement of large systemic arteries in the disease. In addition, we discuss current insights into the immune pathology of GCA and highlight immune cells and cytokines that are associated with clinical outcomes in GCA. Finally, we evaluate open questions and research priorities that need to be solved before precision medicine for GCA patients can become a reality.

Evidence for distinct GCA subsets based on clinical features

Systemic inflammation. Systemic inflammation is present in the vast majority of patients with GCA (8). Symptoms resulting from systemic inflammation may include general malaise, weight loss, night sweats, and low-grade fever. Laboratory findings suggestive of systemic inflammation include elevation of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and thrombocyte count. In addition, anemia due to chronic inflammation is frequently observed in patients with GCA.

With the exception of 3 studies (9–11), a vast number of studies have shown that GCA patients with a strong systemic inflammatory response have a lower risk of cranial ischemic symptoms compared with patients with a weak systemic inflammatory response (Table 1) (12–25). For instance, pretreatment ESRs and CRP levels are inversely correlated with the risk of visual symptoms in GCA (14,17–19,21,22). The presence of fever is also associated with a lower risk of cranial ischemia in GCA patients (16,23).

A possible explanation is that patients with cranial ischemic symptoms present earlier in the disease course and therefore have not yet developed a strong systemic inflammatory response (12,18,23). Although 1 study documented that ESR levels are higher in GCA patients with a longer symptom duration (19), 3 studies showed no clear relationship between the magnitude of the systemic inflammatory response and symptom duration (12,15,26). As an alternative explanation, other investigators have reported that a strong systemic inflammatory response may prevent ischemic events by

directly promoting neoangiogenesis in ischemic tissue (27,28).

With respect to long-term disease outcomes, 4 studies suggested that a strong systemic inflammatory response might be associated with higher relapse rates and glucocorticoid requirements in patients with GCA (9,15,29,30).

Thus, current evidence indicates that the magnitude of the systemic inflammatory response may identify GCA patients with distinct disease outcomes. However, clearly defined criteria for “strong” and “weak” systemic inflammation are lacking. It has been proposed that “strong” systemic inflammation might be defined as the presence of ≥ 3 of the following 4 parameters: fever, weight loss, an ESR of >85 mm/hour, and a hemoglobin level of <11 gm/dl or <6.8 mmoles/liter (9,12,15). Clearly, this definition and its application in stratifying GCA patients need to be validated in protocolized study cohorts with long-term follow-up.

Vasculitis of large systemic arteries. Imaging studies have shown that inflammation of large systemic arteries (e.g., aorta, subclavian arteries, and axillary arteries) is frequently present in patients with GCA (31). In fact, some GCA patients present with vasculitis in these large systemic arteries in the absence of cranial vasculitis. Few studies have investigated the impact of large systemic artery involvement on disease outcomes in GCA. One prospective study and 4 retrospective studies demonstrated a lower risk of cranial ischemic symptoms in GCA patients with large systemic artery involvement, even in patients with positive temporal artery biopsy findings (Table 1) (31–35). In contrast, 1 retrospective study showed a higher risk of cranial ischemia in GCA patients with large systemic artery involvement (30). In the prospective study, large systemic artery involvement had no effect on laboratory markers of systemic inflammation (31). Two retrospective studies suggested that large systemic artery involvement is associated with higher relapse rates and increased requirements for glucocorticoids in GCA (34,36), although this association was not observed in 3 other retrospective studies (35,37,38). It is important to note that in some of the retrospective studies, inflammation of large systemic arteries was not routinely investigated in all of the patients with GCA. Therefore, some patients might have been misclassified as not having large systemic artery involvement.

A general limitation in this context is the lack of a gold standard test for inflammation of large systemic arteries. Different imaging modalities have been used, including ultrasonography, ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -

Table 1. Characteristics predicting cranial ischemia or long-term prognosis in GCA patients*

Characteristic, study	Study design	Cranial ischemia risk	Relapse rate	Glucocorticoid requirement
Strong systemic inflammatory response				
Cid et al, 1998 (12)	Retro	Decreased	NA	NA
Gonzalez-Gay et al, 1998 (13)	Retro	Decreased	NA	NA
Liozon et al, 2001 (14)	Prosp	Decreased	NA	NA
Hernandez-Rodriguez et al, 2002 (15)	Retro	Decreased	Increased	Increased
Gonzalez-Gay et al, 2004 (16)	Retro	Decreased	NA	NA
Salvarani et al, 2005 (17)	Retro	Decreased	NA	NA
Gonzalez-Gay et al, 2005 (18)	Retro	Decreased	NA	NA
Lopez-Diaz et al, 2008 (19)	Retro	Decreased	NA	NA
Nesher et al, 2008 (9)	Retro	No effect	Increased	Increased
Chatelain et al, 2009 (10)	Prosp	No effect	NA	NA
Gonzalez-Gay et al, 2009 (20)	Retro	Decreased	NA	NA
Salvarani et al, 2009 (21)	Retro	Decreased	NA	NA
Martinez-Lado et al, 2011 (29)	Retro	NA	Increased	NA
Muratore et al, 2016 (22)	Retro	Decreased	NA	NA
Liozon et al, 2016 (23)	Prosp	Decreased	NA	NA
Grossman et al, 2017 (24)	Retro	Decreased	NA	NA
Restuccia et al, 2017 (30)	Retro	NA	NA	Increased
De Boysson et al, 2017 (25)	Retro	Decreased	NA	NA
Yates et al, 2017 (11)	Prosp	No effect	NA	NA
Presence of vasculitis of large systemic arteries				
Schmidt et al, 2008 (37)	Retro	NA	NA	No effect
Schmidt et al, 2009 (32)	Retro	Decreased	NA	NA
Prieto-Gonzalez et al, 2012 (31)	Prosp	Decreased	NA	NA
Espitia et al, 2012 (36)	Retro	Increased	Increased	Increased
Czihal et al, 2012 (33)	Retro	Decreased	NA	NA
Muratore et al, 2015 (34)	Retro	Decreased	Increased	Increased
Czihal et al, 2015 (38)	Retro	NA	No effect	NA
De Boysson et al, 2017 (35)	Retro	Decreased	No effect	No effect
Presence of polymyalgia rheumatica				
Myklebust et al, 2001 (44)	Prosp	NA	NA	Increased
Liozon et al, 2001 (14)	Prosp	Decreased	NA	NA
Gonzalez-Gay et al, 2005 (18)	Retro	No effect	NA	NA
Gonzalez-Gay et al, 2009 (20)	Retro	No effect	NA	NA
Liozon et al, 2016 (23)	Prosp	Decreased	NA	NA
Restuccia et al, 2017 (30)	Retro	NA	NA	Increased
De Boysson et al, 2017 (25)	Retro	No effect	NA	NA

* Studies published between January 1, 1997 and January 1, 2018 were included. A strong systemic inflammatory response is defined as an elevated erythrocyte sedimentation rate, elevated C-reactive protein level, decreased hemoglobin level, and/or fever. GCA = giant cell arteritis; Prosp = prospective study; Retro = retrospective study; NA = not assessed.

FDG PET/CT), CT angiography, and magnetic resonance angiography (31,32,34,35). Aortic inflammation may eventually lead to the development of aortic aneurysms and dissection in patients with GCA (39,40). Little is known about the factors predictive of these late complications in GCA, although a recent study indicated that subclavian artery dilatation at diagnosis is associated with a higher risk of aortic aneurysms in GCA patients (41).

Limited data suggest that the presence of large systemic artery inflammation is associated with a lower risk of cranial ischemia, although it is unclear whether the long-term outcomes differ between GCA patients with and those without large systemic artery

involvement. Protocolized cohort studies are required in which all GCA patients are systematically assessed for both cranial and large systemic vasculitis. Importantly, recommendations for the use of imaging in GCA have recently been published (42). Further insight into the development and management of aortic aneurysms is also needed.

Polymyalgia rheumatica (PMR). Patients with GCA may present with clinical signs and symptoms consistent with PMR, a rheumatic syndrome characterized by symmetric pain and stiffness in both the shoulders and hips (1). ¹⁸F-FDG PET/CT scans in these GCA patients often show combined vessel and (peri)articular inflammation (43). Few studies have investigated

the impact of PMR on disease outcomes in patients with GCA. Two studies suggested that coexistent PMR identifies a subset of GCA patients with a low risk of cranial ischemic symptoms (14,23). However, 3 other studies demonstrated no such effect (18,20,25). In addition, 2 retrospective studies showed higher glucocorticoid requirements in GCA patients with concomitant PMR when compared with GCA patients without PMR (30,44). Clearly, current evidence is too contradictory to allow conclusions to be drawn regarding the impact of PMR on cranial ischemic symptoms, whereas limited data suggest that the presence of PMR is associated with a poor long-term outcome.

Evidence for distinct GCA subsets based on immunologic features

In recent years, insight into the immune pathology of GCA has increased considerably. Different histologic patterns have been observed in the temporal arteries of GCA patients. Moreover, complex networks of immune cells and cytokines have been identified in the temporal arteries and blood of GCA patients. The predominance of particular immune cells and cytokines

has been linked to disease outcomes in patients with GCA. Here, we discuss current insights into the immune pathology of GCA. Furthermore, we highlight the immune cells and cytokines that have been linked to poor disease outcomes and that may represent current or possibly future targets for treatment in GCA (Figure 1).

Histologic patterns in temporal artery biopsy specimens. Temporal artery biopsy specimens are frequently obtained during the diagnostic workup of patients with GCA. Distinct histologic patterns of vascular inflammation have been observed in these temporal arteries. Typically, transmural inflammation in all 3 layers of the arterial wall, i.e., the adventitia, media, and intima, is observed (45,46). In recent years, 3 alternative histologic patterns have been observed in temporal artery biopsy specimens: small vessel vasculitis (SVV) limited to periadventitial vessels surrounding a normal temporal artery, vasa vasorum vasculitis (VVV), and inflammation limited to the adventitia. Three studies showed no differences in cranial ischemic symptoms between GCA patients with inflammation limited to the adventitia versus those with transmural

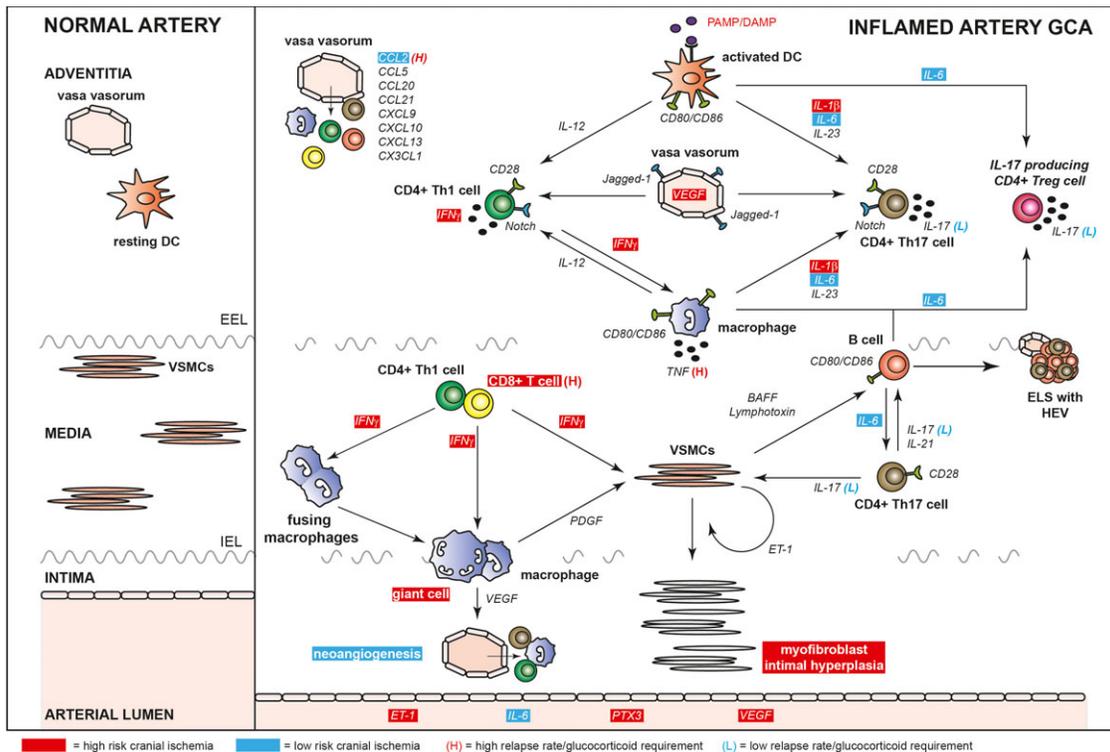


Figure 1. Overview of immune pathology of giant cell arteritis (GCA). Immune cells and cytokines involved in the arterial inflammatory process of GCA and the relationship of these cells and cytokines with disease outcomes in GCA are shown. PAMP = pathogen-associated molecular pattern; DAMP = damage-associated molecular pattern; DC = dendritic cell; IL-12 = interleukin-12; VEGF = vascular endothelial growth factor; IFN γ = interferon- γ ; EEL = external elastic lamina; VSMCs = vascular smooth muscle cells; TNF = tumor necrosis factor; ELS = ectopic lymphoid structure; HEV = high endothelial venule; IEL = internal elastic lamina; PDGF = platelet-derived growth factor; ET-1 = endothelin 1; PTX3 = pentraxin 3.

inflammation (45–47). In addition, various reports indicate that GCA patients with SVV or VVV show similar rates of visual symptoms when compared with GCA patients with transmural inflammation (45,48–50). However, SVV, VVV, and inflammation limited to the adventitia have also been observed in the absence of a convincing diagnosis of GCA, i.e., in patients with PMR, cancer, or infections (47,50–53). Because multiple histologic patterns may coexist within a single temporal artery biopsy specimen from a GCA patient (46,54), it might be possible that SVV, VVV, and inflammation limited to the adventitia are early and nonspecific histologic patterns that may progress to full-blown transmural inflammation in GCA patients. Although it has been suggested that the predominance of these early histologic patterns in a temporal artery biopsy specimen identifies GCA patients with low glucocorticoid requirements (49,55), the clinical relevance of these histologic patterns remains controversial.

Dendritic cells (DCs) and T lymphocytes in the inflamed artery. Vascular DCs reside in the proximity of the vasa vasorum in large and medium-sized arteries (7). Activation of these cells by pathogen-associated molecular patterns or damage-associated molecular patterns, including ligands for Toll-like receptors, may trigger the initial inflammatory response, resulting in chemokine-mediated migration of immune cells via the vasa vasorum (7). Although it has been suggested that varicella zoster virus might be directly involved in the development of GCA (56), a growing number of studies strongly dispute this notion (57–60). DCs stimulate T cells with their cognate peptides bound to class II major histocompatibility molecules, costimulatory molecules (i.e., CD80/CD86), and cytokines. Among these cytokines, interleukin-12 (IL-12) promotes the CD4⁺ Th1 cell response, whereas IL-1 β , IL-6, and IL-23 favor the expansion of CD4⁺ Th17 cells (7). In addition, decreased expression of the checkpoint molecule programmed death ligand 1 on DCs allows ongoing T cell activation in the arterial wall of GCA patients (61–63). In established GCA, macrophages around the external elastic lamina may further stimulate Th1 and Th17 cells by providing costimulation and Th1- and Th2-skewing cytokines. Endothelial cells of the vasa vasorum may further augment Th1 and Th17 cell responses by activating the Notch receptor on these T cells via Jagged-1 (64). Endothelial cells up-regulate Jagged-1 upon exposure to high systemic levels of vascular endothelial growth factor (VEGF) (64).

Th1 and Th17 cells show proinflammatory effects on vascular smooth muscle cells (VSMCs) via

interferon- γ (IFN γ) and IL-17, respectively (65,66). Th1 cells also activate macrophages through IFN γ . IFN γ -producing CD8⁺ T cells, small numbers of which have been detected in the inflamed arteries of GCA patients, might exert effects similar to those of Th1 cells in the vessel wall (67). CD8⁺ T cells may also promote vascular damage through secretion of granzyme B (67). Th17 cells are closely entwined with B cells in the inflamed arteries of GCA patients (66).

Cytokines involved in the Th1 and Th17 cell response have been linked to disease outcome in patients with GCA (Table 2). A previous study showed that high expression of IFN γ in temporal arteries is associated with an increased risk of cranial ischemic symptoms (68). Polymorphisms of the IFN γ gene have been associated with risk of cranial ischemia as well (69). In contrast, another study demonstrated that high local expression of IL-17 is associated with low glucocorticoid requirements in patients with GCA and a trend for lower relapse rates (70). Strong local expression of the Th17 cell-polarizing cytokine IL-6 has been associated with a low risk of cranial ischemia while showing no effect on long-term glucocorticoid requirements (28,71). In contrast, strong expression of IL-1 β in inflamed temporal arteries was linked to an increased risk of cranial ischemia (68). Thus far, the numbers of Th1 or Th17 cells in inflamed temporal arteries have not been linked to disease outcomes in GCA patients. However, a recent study demonstrated that a relatively high number of arterial CD8⁺ T cells (i.e., >6% of infiltrating cells) is associated with an increased risk of cranial ischemia and greater long-term glucocorticoid requirements in GCA patients (67). All of these findings, however, still await validation in protocolized cohort studies.

Macrophages in the inflamed artery. Whereas macrophages around the external elastic membrane are potent producers of Th1- and Th17-polarizing cytokines (Figure 1), macrophages around the internal elastic membrane are involved in vascular damage and remodeling (7). Macrophages produce tumor necrosis factor (TNF) in the inflamed arteries of patients with GCA, and this was linked to high relapse rates in a previous study (71). Macrophages around the internal elastic membrane are activated by Th1 cells and CD8⁺ T cells and develop into multinucleated giant cells under the influence of IFN γ (68). The presence of giant cells was associated with an increased risk of cranial ischemia in 2 studies (10,22), and also tended to correlate with more cranial ischemic symptoms in a

Table 2. Temporal artery biopsy findings associated with the risk of cranial ischemia, the relapse rate, and/or the glucocorticoid requirement in GCA*

Temporal artery biopsy finding, study	Cranial ischemia risk	Relapse rate	Glucocorticoid requirement
Giant cell presence			
Armstrong et al, 2008 (72)	No effect	No effect	No effect
Chatelain et al, 2009 (10)	Increased	NA	NA
Muratore et al, 2016 (22)	Increased	NA	NA
CD8+ T cells†			
Samson et al, 2016 (67)	Increased	NA	Increased
Intimal hyperplasia			
Kaiser et al, 1998 (73)	Increased	NA	NA
Makkuni et al, 2008 (77)	Increased	NA	NA
Neovascularization			
Cid et al, 2002 (27)	Decreased	NA	NA
CCL2†			
Cid et al, 2006 (83)	Decreased	Increased	Increased
ET-1†			
Lozano et al, 2010 (85)	No effect	NA	NA
IFNγ†			
Weyand et al, 1997 (68)	Increased	NA	NA
IL-1β†			
Weyand et al, 1997 (68)	Increased	NA	NA
Hernandez-Rodriguez et al, 2004 (71)	NA	NA	No effect
IL-6†			
Hernandez-Rodriguez et al, 2003 (28)	Decreased	NA	NA
Hernandez-Rodriguez et al, 2004 (71)	NA	NA	No effect
IL-17†			
Espigol-Frigole et al, 2013 (70)	NA	No effect	Decreased
TNF†			
Hernandez-Rodriguez et al, 2004 (71)	NA	NA	Increased

* Studies published between January 1, 1997 and January 1, 2018 were included. GCA = giant cell arteritis; NA = not assessed; ET-1 = endothelin 1; IFN γ = interferon- γ ; IL-1 β = interleukin-1 β ; TNF = tumor necrosis factor.

† High number of cells or protein expression level.

third study (72). Macrophages and giant cells near the internal elastic membrane may secrete platelet-derived growth factor (PDGF) and VEGF, which activate VSMCs (73,74). VEGF also promotes local formation of neovessels (75). These neovessels allow for direct entry of immune cells into the deeper layers of the arterial wall. Nevertheless, one study showed a lower incidence of cranial ischemic symptoms in patients with neovessels in their temporal artery biopsy specimens (27).

VSMCs in the inflamed artery. VSMCs are central players in the immune pathology of GCA. Activated VSMCs migrate toward the intima and differentiate into myofibroblasts (74,76). The latter cells may proliferate extensively, thereby resulting in intimal hyperplasia and luminal narrowing (73). Intimal hyperplasia has been linked to secretion of PDGF by macrophages and is strongly associated with the occurrence of cranial ischemic symptoms (73,77). A recent study demonstrated that activated VSMCs may secrete BAFF and lymphotoxin, which promote the development of ectopic lymphoid structures in the inflamed arterial wall (66).

B cells and ectopic lymphoid structures in the inflamed artery. B cells are present predominantly in the adventitia of GCA patients and may form ectopic lymphoid structures together with T cells, follicular DCs, and high endothelial venules (66,78,79). Ectopic lymphoid structures are known to facilitate chronic inflammation by providing a framework for continuous B cell and T cell activation. Costimulatory molecules and cytokines such as IL-21 and IL-6 are likely to be involved in this process (66,78). Ectopic lymphoid structures are more frequently observed in GCA patients with strong systemic inflammation, but show no relationship with the occurrence of cranial ischemic symptoms (66).

Chemokines in the inflamed artery. Immune cells and VSMCs secrete a wide variety of chemokines that attract different types of immune cells to the arterial wall of GCA patients (65,66). Th1 and CD8+ T cells are attracted by CXCL9 and CXCL10 (67), and Th17 cells are attracted by CCL20 (80). Monocytes enter the arterial wall under the influence of CCL2 and CX3CL1 (81), after which these cells differentiate into proinflammatory macrophages. B cells may migrate toward CCL20 and CXCL13 gradients in the

arterial wall (66,80). CCL5 promotes migration of both T cells and monocytes toward inflamed arteries (82). Little is known about the impact of local chemokine expression on clinical outcomes in GCA. Only one study showed that strong up-regulation of CCL2 in temporal arteries is associated with a low risk of cranial ischemic symptoms, but higher relapse rates and glucocorticoid requirements (83).

Systemic cytokines. The levels of many proinflammatory cytokines are increased in the peripheral blood of GCA patients (84). Circulating levels of several cytokines have been identified as potential predictors of cranial ischemic symptoms in GCA (Table 3). In a previous study, high levels of systemic IL-6 were observed in GCA patients with a low incidence of cranial ischemic symptoms (28). This finding is consistent with the lower risk of cranial ischemia in patients with a strong systemic inflammatory response (Table 1), because IL-6 also drives the acute-phase reactant CRP (15). It has been suggested that systemic IL-6 may directly promote angiogenesis in the ischemic end organs of GCA patients (28). In contrast, high systemic levels of endothelin 1 (ET-1), pentraxin 3, and VEGF have been linked to an increased risk of cranial ischemia (85,86). Genetic variants of the VEGF gene have also been associated with the risk of cranial ischemic symptoms (87).

Perspectives

Even though further studies are required to establish immunologic subsets of GCA patients, and correlations are not proof of causality between immunologic changes and disease outcomes in GCA, identification of immunologic subsets might provide a rationale for targeted treatments.

Targeting factors associated with cranial ischemic symptoms. Current evidence indicates that vascular predominance of IFN γ , IL-1 β , VEGF, and CD8+ T cells, as well as the presence of multinucleated giant cells and intimal hyperplasia, identify GCA patients with a high risk of cranial ischemic symptoms (Figure 1 and Table 2). Therefore, treatments directly or indirectly targeting these cytokines or immune cells are interesting to study.

Anti-IFN γ treatment was shown to ameliorate vascular inflammation in an experimental model of GCA (65). In addition, anti-IL-12/23 therapy was demonstrated to inhibit the induction of IFN γ -producing Th1 cells (88). Anti-IL-12/23 therapy showed promising therapeutic effects in a case series of GCA patients (89). Consequently, a randomized controlled trial with anti-IL-12/23 therapy was recently initiated (ClinicalTrials.gov identifier: NCT02955147). In addition, targeting of the IFN γ response will likely ameliorate the effects of CD8+ T cells while also limiting formation of multinucleated giant cells. Furthermore, CTLA-4Ig and JAK inhibitors will also limit activation of Th1 and CD8+ T cell responses in patients with GCA. A recent randomized controlled trial demonstrated the efficacy of CTLA-4Ig for the maintenance of remission in patients with GCA (6). Currently, a single-center trial of the JAK inhibitor baricitinib in GCA is ongoing (ClinicalTrials.gov identifier: NCT03026504). Another JAK inhibitor, tofacitinib, also ameliorated vascular inflammation in an experimental model of GCA (90). The same holds true for stress-associated endoplasmic reticulum protein 1, a myxoma virus-derived serpin (91). The IL-1R antagonist anakinra has shown promising results in a case series of GCA patients (92) and will be investigated in a randomized controlled trial (ClinicalTrials.gov identifier:

Table 3. Serum or plasma proteins associated (when elevated) with the risk of cranial ischemia, the relapse rate, and/or the glucocorticoid requirement in GCA*

Serum/plasma protein, study	Cranial ischemia risk	Relapse rate	Glucocorticoid requirement
ET-1			
Lozano et al, 2010 (85)	Increased	NA	NA
IL-6			
Hernandez-Rodriguez et al, 2003 (28)	Decreased	NA	NA
IL-1 β			
Hernandez-Rodriguez et al, 2003 (28)	No effect	NA	NA
PTX3			
Baldini et al, 2012 (86)	Increased	NA	NA
TNF			
Hernandez-Rodriguez et al, 2003 (28)	No effect	NA	NA
VEGF			
Baldini et al, 2012 (86)	Increased	NA	NA

* Studies published between January 1, 1997 and January 1, 2018 were included. GCA = giant cell arteritis; ET-1 = endothelin 1; NA = not assessed; IL-6 = interleukin-6; PTX3 = pentraxin 3; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

NCT02902731). Although high systemic levels of VEGF have been associated with cranial ischemic symptoms in GCA patients, anti-VEGF treatment might potentially be dangerous, because this treatment may inhibit angiogenesis in the ischemic tissue of GCA patients (e.g., the eyes). Intimal hyperplasia develops under the influence of PDGF and ET-1. Anti-PDGF treatment was shown to effectively inhibit intimal hyperplasia in a temporal artery explant model (74). Blocking ET-1 reduced the outgrowth of VSMCs in another experimental study (76). Therefore, various immune cells and cytokines associated with cranial ischemic events are potential targets for therapy in patients with GCA.

Targeting factors associated with relapse and high glucocorticoid requirement. A strong systemic inflammatory response as well as high local expression of CCL2 and TNF have been associated with the development of relapse and/or increased glucocorticoid requirements in GCA patients (Tables 1 and 2). Although the prognostic value of systemic levels of IL-6 in long-term outcomes in GCA patients has not been formally studied, it is likely that GCA patients with a strong systemic inflammatory response also demonstrate the highest levels of systemic IL-6. Therefore, GCA patients with disease relapses and an increased glucocorticoid requirement could potentially benefit from IL-6–targeting treatment. Indeed, randomized controlled trials showed that anti-IL-6R therapy effectively maintained glucocorticoid-free remission in a significant proportion of patients with GCA (4,5). Anti-CCL2 treatment has not yet been tested in GCA patients or experimental models of GCA. Randomized controlled trials have demonstrated that anti-TNF

therapy lacks therapeutic efficacy in GCA (93,94).

Open questions and research priorities

Evidence for distinct subsets of GCA patients is based mostly on retrospective cohort studies. Important questions regarding disease subsets in GCA are summarized in Table 4. Clearly, current evidence for distinct disease subsets of GCA patients requires validation in protocolized cohort studies with well-characterized GCA patients. Evidence for disease subsets might be further obtained by post hoc analyses of the large randomized controlled trials in patients with newly diagnosed GCA (4,6,93–97). Although data on large vessel involvement have not been routinely obtained in these trials, baseline data on inflammation markers and the presence of PMR have been recorded. Eventually, dedicated randomized controlled trials are required to evaluate the effects of targeted treatments in distinct subsets of GCA patients, as was recently proposed for patients with small vessel vasculitis (98).

Conclusions

Ample evidence indicates that GCA is a clinically and immunologically heterogeneous autoimmune disease. However, patients with GCA are currently treated according to standardized regimens. Retrospective studies have identified several clinical and immunologic characteristics associated with cranial ischemia and long-term disease outcomes in GCA. Future studies should validate prognostic factors and the presence of disease subsets in GCA. Eventually, recognition of distinct GCA disease subsets may be helpful for implementing precision medicine for GCA patients.

Table 4. Open questions regarding disease subsets in GCA*

1. What criteria can be used to identify GCA patients at high risk of severe cranial ischemic events?
2. What criteria should be used to identify GCA patients with a strong systemic inflammatory response that appears to be associated with a decreased risk of cranial ischemic events?
3. What are the optimal laboratory methods, or perhaps imaging methods, to measure immunologic markers in the tissue or blood of GCA patients, and which are the optimal prognostic cutoff levels for these markers?
4. In order to personalize the long-term management of GCA, what criteria identify patients who are prone to develop future relapses, ischemic events, or aortic aneurysms?
5. Which immune cells or cytokines associated with poor long-term disease outcomes should be targeted by treatment in GCA patients?
6. Are measurements of immunologic cells or cytokines predictive of the response to treatments targeting these cells or cytokines?

* GCA = giant cell arteritis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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