MANAGEMENT OF CORTICOSTEROID RESISTANT GIANT CELL ARTERITIS

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ABSTRACT

Giant cell arteritis is one of the most common forms of primary systemic vasculitis. Although corticosteroids are still the mainstay of treatment, a significant number of patients suffer from serious complications of the disease or its therapy, and many patients suffer relapses. The evidence for the effectiveness of conventional immunosuppressive therapy is limited. A better understanding of the pathogenetic mechanisms may lead to a more rational approach to therapy in future.

Keywords: Giant cell arteritis; Corticosteroids; Methotrexate; Azathioprine; Cytokines; Therapy

RESUMO

A arterite de células gigantes é uma das mais comuns vasculites primárias sistémicas. Apesar dos corticosteróides serem ainda a principal terapêutica, um número significativo de doentes sofre complicações graves da doença ou da terapêutica e muitos sofrem recidivas. A evidência de eficácia das terapêuticas convencionais imunossupressoras é limitada. Um melhor entendimento dos mecanismos patogénicos poderá conduzir a uma terapêutica mais racional no futuro.

Palavras-Chave: Arterite de células gigantes; Corticosteróides; Metotrexato; Azatioprina; Interleucinas; Terapêutica

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Abbreviations

CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
GCA	Giant cell arteritis
IFN gamma	Interferon gamma
IL-1	Interleukin 1
IL-2	Interleukin 2
IL-6	Interleukin 6
PDGF	Platelet derived growth factor
PMR	Polymyalgia rheumatica
TIA	Transient ischaemic attack
TNF alpha	Tumour necrosis factor alpha
VEGF	vascular endothelial growth factor

Introduction

Giant Cell Arteritis (GCA) is a granulomatous inflammatory vasculitis which affects medium to large sized blood vessels, most commonly involving the cranial arteries. It is the most frequently occurring vasculitic disorder, often presenting in the 7th and 8th decades with an estimated incidence of 15-25 per 100,000 in at-risk populations[1]. It affects women twice as often as men[2]. The classical presenting features are those of unilateral temporal headache which may be associated with scalp tenderness, jaw claudication, malaise and fever. The most feared complication is that of partial or complete loss of vision, most commonly caused by anterior ischaemic neuropathy of the optic nerve, due to involvement of the ophthalmic or posterior ciliary arteries. This is reported in up to 20% of cases of GCA[2]. Other neurological sequelae include peripheral neuropathy, transient ischaemic attack (TIA) and stroke. There is an increased risk of thoracic and abdominal aortic aneurysms, estimated at 17.3 and 2.4 times respectively compared to normal[3]. Aortic dissection, aortic rupture, and aortic valve insufficiency may also occur. GCA is closely related to polymyalgia rheumatica (PMR), which causes aching and morning stiffness of the proximal limb and joint regions, and indeed both conditions often coexist clinically.

Laboratory investigations typically reveal a markedly increased erythrocyte sedimentation rate (ESR), although this parameter may be normal in a small proportion at the time of presentation[4]. CRP is usually also elevated, and a normocytic anaemia is common. Temporal artery biopsy is recommended to aid diagnosis, and demonstates a patchy granulomatous inflammation with intimal thickening, usually with the presence of multinucleate giant cells. However, the biopsy may be normal due to the patchy distribution of inflammation in affected cases. Abnormal areas are called «skip lesions», and may be surrounded by completely normal tissue, thus requiring careful, fine sectioning of the tissue samples in order to ensure that these areas are not overlooked. Age related changes to vessel walls may cause confusion, as may the effects of corticosteroids given prior to the biopsy, resulting in healing of the inflammation. Ideally, a biopsy should be taken within one week of initiating treatment with steroids[5].

Corticosteroid Treatment In GCA

The traditional treatment of suspected GCA is with oral corticosteroids, which in most cases leads to remission of clinical symptoms. A daily regimen is recommended, and indeed alternate day steroid dosing seems ineffective in controlling disease symptoms[6]. High starting doses are recommended to establish optimum disease control. Kyle and Hazleman examined 35 patients with GCA, 20 of

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whom were treated with a high dose steroid regime (40mg for 4 weeks, reduced to 20mg by 2 months). The remaining 15 were randomly assigned to a lower dose regime (40mg for 5 days, reduced to 10mg by 2 months). The low dose regimen was associated with clinical relapse in 40% of cases (6/15), whereas the high dose regimen led to relapses in only 20% of cases (4/20)[7]. Although there have been suggestions that lower doses of corticosteroids may be sufficient for most cases of GCA[8], it is common practice to initiate a high dose (40-60mg/day) of prednisolone[9] for 2 to 4 weeks, followed by dose tapering. The optimum duration of therapy is debated but for most patients up to 2 years of treatment is advised[10].

Pathological Mechanisms

The inflammation found in GCA penetrates all layers of the arterial wall, and the infiltrates consist predominantly of T-Cells and monocytes/macrophages, often arranged in granulomata. In about 50% of cases, multinucleate giant cells are formed, and these reside close to the disrupted internal elastic lamina[11]. An antigen –driven immune response with the local production of specific pro-inflammatory cytokines has been postulated[11]. CD4 T lymphocytes may be stimulated by antigen within the adventitia, where they accumulate, having gained access via the vasa vasorum. These T cells secrete IFNα, which regulates macrophage differentiation and cytokine production, and formation of giant cells. Macrophage secretion appears to have a geographical determination, such that those in the adventitia produce the pro-inflammatory cytokines IL-1, IL-6, and TNF-α, whereas those in the media produce metalloproteinase-2, and those in the intima secrete nitric oxide synthase-2[11]. These latter products are responsible for the local destruction of the internal elastic lamina, by oxygen radical mediated tissue injury[11]. This is balanced by intimal hyperplasia which represents a direct response to this tissue injury. Macrophages and giant cells at the media-intima border produce platelet-derived growth factor (PDGF)[12], and the formation of new vasa vasorum is characteristic in inflamed temporal arteries, as a response to vascular endothelial growth factor (VEGF) secretion[11]. These growth and angiogenic factors released by macrophages therefore regulate the process of intimal hyperplasia[1], which may account for the ischaemic complications of GCA, via vessel occlusion.

The triggering antigen in GCA remains unclear, although an infective aetiology has been suggested on the basis of detection of *Chlamydia pneumonia* DNA in temporal artery specimens of 8 of 9 patients with GCA[13]. Parvovirus B19 has also been postulated as an infectious agent[14]. However these findings have not been replicated in a further study of 30 cases of suspected GCA, 12 confirmed on biopsy[15].

Tissue cytokine expression varies between patients, and the patterns of expression broadly correlate to differing clinical phenotypes[16]. IFN-α in particular is raised disproportionately in patients with evidence of jaw claudication and visual loss[16], and may be a potential future therapeutic target.

IL-6 deserves special mention, since plasma levels have been shown to reflect disease activity. In a study of 25 patients with biopsy-proven GCA, 92% of patients had elevated IL-6 levels at presentation, compared to only 76% with a raised ESR. Patients were treated with a predetermined tapering course of steroids, and ESR was normalised in 95.5% of cases post treatment, whereas, IL-6 levels normalised in only 45.5% of cases During steroid tapering, 60% of patients developed recurrent disease. In 89% of these recurrences, IL-6 levels were increased, whereas the ESR was elevated in only 58% of cases. In addition, IL-6 remained elevated in 68% of patients considered clinically to be in remission[17]. It is possible that IL-6 may have additional beneficial effects in GCA, bearing in mind its ability to downregulate monokine production, notably IL-1 and TNF-α[16]. Indeed, one study showed that lowered IL-6 mRNA levels were present in patients with ischaemic complications, such as visual loss and stroke, when compared to patients without such manifestations[18], also suggesting a potentially protective role.

Finally, there is evidence that the strength of the initial inflammatory response may be useful in determining corticosteroid requirements in GCA. In a retrospective observational study of 75 patients with biopsy-proven GCA, Hernandez-Rodriguez et al grouped cases into those with strong inflammatory response, and those with a weak one, based on the presence of fever, weight loss, raised ESR and anaemia. Those patients with strong inflammatory responses had significantly higher circulating levels of both TNF-α and IL-6 than those with weak

Quadro 1. Summary of the Potential Pathogenetic Mechanisms Involved in Giant Cell Arteritis, Starting from the Migration of Immunocompetent Cells through the Adventitia Leading to Vessel Narrowing and Occlusion

Site	**Adventitia**	**Media**	**Intima**	**Lumen**
Cells	Macrophages, T cells (typically CD4+ predominance)	Macrophages; giant cells	Macrophages	
Mediators	IFN gamma TNF alpha IL6, IL1	Platelet derived growth factor; vascular endothelial growth factor	Nitric oxide synthase -2; Platelet derived growth factor; vascular endothelial growth factor	
Putative events	Invasion through vasa vasorum by T cells and macrophages (attracted by local antigen deposition?)	In situ production of cytokines and activation of immunocompetent cells; new vessel formation	Destruction and subsequent proliferation of intima as an attempt and new vessel formation	Narrowing, occlusion; ischaemic consequences

responses, and furthermore, this group of patients required a median of 62 weeks to reach maintenance doses of <10mg prednisolone per day, compared to 40 weeks in the group with weak responses. Disease flares were also more common in the strong response group[19]. In patients with strong inflammatory responses, raised circulating TNF-α levels are predictive of the need for longer duration steroid therapy[20]. It seems therefore that as well as providing a marker of disease activity, IL-6 and TNF-α may be useful in predicting corticosteroid requirements in GCA, and could help to determine how refractory a case is likely to be to steroid treatment.

Table 1 summarises our current understanding of the immunopathogenensis of giant cell arteritis.

Corticosteroid-Resistant Giant Cell Arteritis

The relatively long term use of steroids, and the initial high doses required are associated with many potential adverse side-effects. Kyle and Hazleman showed that steroid related complications occurred in up to 36% of treated patients, and included fractures, peptic ulcer disease, development of diabetes, peripheral oedema, cataract formation, and infections. These side effects were significantly more common in patients treated with an initial high dose of prednisolone of more than 30mg per day, and in those in whom treatment was continued for many years at a dose of more than 5mg per day[21]. Nesher et al showed that over a 15 year period, 58% of treated patients with GCA had serious steroid-related complications, most frequently in the over 75 age group, and in those treated with an initial dose of more than 40mg per day[22]. Proven et al observed adverse events in 86% of 120 patients treated with steroids for GCA, and in 58% of these cases, two or more adverse side-effects were noted[23]. Although these data include patients treated prior to the widespread introduction of bone protection to avoid steroid-related osteoporosis, it is clear that given the high frequency of steroid-related adverse events, other less toxic treatment strategies are needed.

Corticosteroids do not completely suppress clinical or serological evidence of disease activity in GCA. Up to 60% of treated patients experience disease relapse on tapering of steroid dose[17], and in addition, between 30 to 50% of patients have spontaneous relapses, independent of the steroid regimen used[2]. Kyle and Hazleman found that 8 out of 18 patients with GCA, and 11 out of 17 patients with both GCA and PMR experienced at least one relapse at 2 months after steroid treatment. Further relapses were most common in the first year of treatment, and 54% occurred in association with reduction of the steroid dose[24]. The authors noted that the greatest risk of relapse was amongst patients with both GCA and PMR. Andersson et al followed 90 patients with GCA for a period of 9-16 years after diagnosis. The clinical relapse rate was 47%, and 96% of these occurred within the first year

of treatment. 55% occurred on a daily prednisolone dose of 5mg or less. After 9 years, 15% of patients still required prednisolone treatment, suggesting a more chronic disease pattern in some patients mandating very long term steroid use[25]. Hayreh and Zimmerman found that the median time to reach the lowest maintenance dose of prednisolone where the ESR and CRP stayed stable or went lower was 48.7 months[26]. Persistent active vasculitis has been reported at post mortem in temporal and carotid artery specimens from a patient who had died from a non-arteritic myocardial infarction. The patient had been treated with corticosteroids for biopsy-proven GCA diagnosed 6 weeks earlier, and had clinical and laboratory evidence (normalised ESR) of disease suppression[27]. This suggests that clinical symptoms and ESR are not enough to predict the duration of active arteritis, and the response to steroid therapy. It is widely accepted that the ESR can be normal in active GCA both at the time of diagnosis[2] and during relapses[28]. As well as using IL-6 levels to monitor disease activity as discussed above, levels of anticardiolipin antibody have been shown to predict disease flares and relapses in patients with biopsy-proven GCA[29]. With respect to identifying patients likely to experience more severe disease, who may need longer durations of steroid treatment, it has been shown that a reduced percentage of circulating CD8+ T cells, measured after six months of treatment is predictive of longer duration of corticosteroid treatment, greater cumulative doses of steroid treatment, and more frequent relapses compared to patients with levels in the normal range[30]. The level of soluble IL-2 receptors remains elevated despite clinical disease remission[30]. Reduced levels of von-Willebrand factor antigen are reported in some patients with GCA in long-lasting remission, suggesting that this marker may aid decisions with respect to withdrawal of steroid treatment[31].

Complications of GCA include loss of vision, most frequently due to anterior ischaemic optic neuropathy, and vasculitic cerebrovascular accident, commonly affecting the vertebro-basilar circulation. In a retrospective study by Gonzalez-Gay et al of 239 patients with biopsy-proven GCA, visual involvement, including diplopia and transient visual loss was seen in 69 patients. Of these patients, 34 developed permanent visual loss, 8 of whom showed partial improvement with corticosteroid therapy. Transient visual loss was the best predictor of permanent visual loss, but jaw claudication, normal liver enzyme levels and lack of constitutional symptoms were also indicators of risk[32]. Interestingly, the authors noted that the only predictor of treatment success was early initiation of therapy, although pulsed iv corticosteroids offered no additional benefit. In the same study, 8 patients developed stroke, 7 of whom were receiving steroid therapy[32]. Permanent visual loss and jaw claudication were predictors of stroke, supporting the notion that these ischaemic complications are consequences of luminal narrowing secondary to intimal hyperplasia. A further potential risk factor for permanent visual loss appears to be the presence of thrombocytosis, suggesting a role for platelet inhibitors[33,34]. However, the absence of high ESR values and systemic manifestations may still be also associated with this complication[34]. Hayreh et al examined 84 patients with biopsy-proven GCA and visual loss, 41 of whom were treated with intravenous, then oral steroids, 43 of whom received oral steroids only. Overall, improvement was demonstrated in only 4% of eyes with visual loss, and only when steroid therapy had been started within 3-4 days of the visual loss. There was no significant difference between the two treatment regimes, with visual improvement demonstrated in three of the 41 patients (7%) receiving initial intravenous steroid therapy compared to two of the 43 (5%) in the oral steroid group[35]. The same authors have shown that only a minority of patients (4%) with visual loss treated with high dose steroids develop further visual deterioration, and this occurred within 5 days of treatment initiation[26]. Although these data are non randomised and retrospective, there is a suggestion that early high dose steroids may influence further visual loss. In conclusion therefore, permanent loss of vision is a significant cause of morbidity in patients with GCA, which may be prevented but not usually ameliorated by early steroid therapy.

Management of Resistant Cases

In apparently resistant cases of GCA, it is important to review the accuracy of the diagnosis of GCA. Whilst lymphoproliferative disorders can mimic GCA clinically, other vasculitides such as polyarteritis nodosa and Wegeners granulomatosis may involve the temporal artery leading to vascu-

lar inflammation on biopsy[10], and infections and occult malignancy may cause malaise and raised inflammatory markers. The use of alternative agents to treat GCA is of increasing clinical interest, given the side–effects of long-term corticosteroid use, the frequency of disease relapse, and the consequences of uncontrolled disease.

Pulse intravenous steroids

The use of an initial intravenous pulse of steroids in simple forms of GCA has been examined as a steroid-sparing strategy. In a study of 164 patients, patients were randomized to receive a 240mg iv pulse of methyprednisolone, followed by prednisolone at a dose of either 0.7mg/kg/day or 0.5mg/kg/day or simply prednisolone alone. No difference was found in terms of the time required for normalisation of CRP, the frequency of corticosteroid resistance (13.5% of cases), and corticosteroid related side-effects (39% of cases)[36]. Despite the fact that Hayreh and Zimmerman found no additional benefit of intravenous over oral steroid therapy for preventing visual loss in GCA, the authors still recommend treating with one intravenous pulse (equivalent to one gram of prednisolone), followed by high dose steroids if a history of amaurosis fugax is present, if there is complete loss of vision in one eye, or if there are early signs of involvement in the second eye[26].

Cyclophosphamide

The use of cyclophosphamide for treating GCA is limited to case reports. De Vita et al describe 4 patients in whom pulsed intravenous cyclophosphamide was used to treat GCA. In three cases, two of whom had been treated with prior corticosteroids low dose weekly cyclophosphamide was used in addition to steroids (0.5g weekly for 3 weeks), in order to minimise cumulative steroid dose, in view of the existence of concomitant pathologies, such as osteoporosis and severe hypertension. In the fourth case, the disease had relapsed twice whilst on steroid treatment, and steroid induced side effects had developed, and so a higher dose of cyclophosphamide was administered (0.5g per day for 5 days, then 1g after 15days). All four patients demonstrated good clinical and laboratory responses, and rapid steroid tapering was possible. No significant adverse side–effects were noted in these patients[37]. Clearly, further studies are needed to clarify the role of cyclophosphamide in treating GCA, especially given that the improvement in two of the patients described above may be attributable to the steroids that were given together with the cyclophosphamide.

Azathioprine

Azathioprine has been used as a steroid-sparing agent in the treatment of GCA[38]. 31 patients with GCA, PMR or both, whose disease had been controlled on 5mg or more of prednisolone for a period of at least three months, were randomised to either azathioprine 50mg three times a day or placebo, and were followed up at 4 weekly intervals over a period of 52 weeks. 22 patients completed the study, but despite these small numbers which limit the trial, the steroid requirement in the azathioprine treated group was less than in the control group (1.9+/- 0.84mg vs 4.2+/- 0.58mg), but only at 52 weeks. 7 patients from the azathioprine group were withdrawn due to nausea, vomiting and diarrhoea, but none had biochemical or haematological disturbances[38]. Despite the fact that this study suggests that azathioprine may have a role in patients who need high doses, or long durations of steroid therapy, the patient numbers are low, the reduction in steroid dose is small, and azathioprine was associated with the development of intolerable adverse effects.

Methotrexate

The most robust evidence for the role of methotrexate in controlling disease in GCA comes from two randomised, double-blind, placebo-controlled studies. Jover et al[39] studied 42 patients with biopsy-proven GCA, who had been initially treated with high dose prednisone 60mg/day, tapered to 40mg after one month, 20mg after 2 months, and thereafter by 2.5mg every 2 weeks, based on clinical disease activity. At the same time, 10mg of methotrexate or placebo was started on diagnosis, and maintained throughout the treatment period, and discontinued after 24 months of follow-up if clinical signs of disease activity were absent. The rate of disease relapse was lower in the methotrexate group (45% cf 84.2%), and interestingly, the re-

lapses in this group tended to be less severe compared to controls. Relapses also occurred later than in control cases, and at a lower dose of prednisone. Furthermore, the mean duration of steroid therapy was 29 weeks in the methotrexate group, as opposed to 94 weeks in controls, due to the improved disease control in this group. No difference was noted in the overall rate of occurrence of adverse events between the two groups, but three patients did experience adverse events whilst on methotrexate, which was subsequently stopped. These included pancytopaenia, mucositis, and oral ulcers[39]. The authors conclude that methotrexate represents an effective treatment for controlling disease activity, whilst providing a significant steroid-sparing effect.

The second study is a multicenter study, which enrolled 98 patients. Patients were all given 1mg/kg/day of prednisone, with a maximum dose of 60mg/day, tapered after one month, such that after 3 months the dose was 60mg on alternate days. Cases were randomised in addition to receive either 0.15mg/kg/week of methotrexate (this was increased to a maximum of 0.25mg/kg, or 15mg/ /week), or placebo, and therapy was continued until 12 months after the achievement of remission. 57.5% of those in the methotrexate group failed therapy after one year (as defined by 2 distinct disease relapses, or a relapse not ameliorated by increasing the prednisone dose), compared to 77.3% of the control group[40]. This result did not reach statistical significance. In addition, there were no significant differences with regard to cumulative corticosteroid dose, or treatment toxicity.

The conflicting results of the two major trials may in part be due to the difference in tapering of corticosteroids, with a much more aggressive steroid tapering regimen in the second study. There were differences in definitions of disease relapse between the 2 trials, using recurrence of clinical symptoms[39], or the presence of clinical symptoms combined with a raised ESR[40] respectively. The length of follow up was more than one year in the Hoffman et al study, but 2 years in the Jover et al study. Although the first study suggests benefit from using methotrexate, it is important to note that despite reducing the steroid requirements in the experimental group, this was not enough to reduce the incidence of drug-related adverse events, which is an important outcome measure to consider. In conclusion, methotrexate may offer an adjunct to corticosteroid therapy in resistant cases of GCA, but evidence so far is conflicting, and further studies are needed before clear recommendations are made.

Anti-TNF-α Agents

TNF-α, as discussed above, is released from activated macrophages in patients with GCA, and has been reported to correlate with the intensity of the initial systemic inflammatory response in patients with GCA[19]. Data for the use of anti-TNF-α agents in GCA is limited to a handful of published cases, but of great interest, since these agents may offer more rational therapy for corticosteroid-resistant cases. Treatment with both infliximab, a chimeric monoclonal antibody to TNF-α, and etanercept, a TNF-α receptor fusion protein, has been reported with encouraging results. Cantini et al report four cases of severe GCA, who had all relapsed on reduction of the steroid dose to 7.5-12.5mg per day, and who had also all experienced steroid-related adverse effects. All patients received 2 iv infusions of infliximab (3mg/kg administered over a two hour period) at weeks 0 and 2, and a further infusion at week 6 only if clinical remission had been achieved after the second dose. For the first two weeks of therapy, patients received 5mg prednisolone per day, and this was stopped if remission was shown after two infusions. In three out of the four cases, complete remission was achieved, both in terms of clinical symptoms, and ESR/CRP reduction. This persisted after the third infusion, and was still evident at 5 months follow up [41]. Significantly, no adverse effects to infliximab were noted. A further case resistant to large doses of corticosteroids alone, or in combination with either azathioprine or methotrexate, was treated with 5 infusions of infliximab (3mg/kg dosing) given at 0, 2, 6, 14, and 22 weeks in addition to prednisolone and methotrexate. Marked improvement was a noted in symptoms and acute-phase markers[42]. Etanercept was effective in one case of an elderly male with GCA, resistant to high doses of steroids, who had developed a TIA associated with a raised ESR. Symptoms resolved and prednisolone was reduced to 5mg per day. Interestingly, when the patient failed to take etanercept as instructed, the disease relapsed, but re-induction of remission was possible on re-starting the etanercept along with an increase in the steroid dose[43]. Clearly, despite the encouraging results suggested

in these reports, large randomized controlled trials are required to test the effectiveness of this promising strategy.

Aspirin

Aspirin may have a role in the management of GCA in preventing ischaemic complications. Acute visual loss and cerebrovascular accidents cause much morbidity in GCA, and may occur as a presenting feature of disease, or during disease relapses. Nesher et al retrospectively examined 175 cases of GCA, 36 of whom were already taking 100mg/day of aspirin for known ischaemic heart disease. The occurrence of cranial ischaemic complications at presentation, including CVA and visual loss was noted in 8% of aspirin-treated patients, and 29% of non-aspirin treated ones. This was despite the higher frequency of cardiovascular risk factors amongst the aspirin treated individuals. Treatment with high dose steroids was begun, and aspirin was started in an additional 41 cases by individual physicians for presumed beneficial effect. Despite steroid treatment, cranial ischaemic complications were still more common in those not taking aspirin, with an occurrence rate of 3% (aspirin treated) versus 13% (non-aspirin treated)[44]. The authors conclude that despite possible confounding factors, including the likely use of statins in the patients with heart disease, the benefit of aspirin in decreasing the rate of cranial ischaemic complications in GCA is likely to be real. In addition to its well documented anti-platelet properties, Weyand et al[45] have shown that aspirin at a dose of 20-100mg/kg, especially in combination with steroids, suppresses IFN-α production in inflamed temporal arteries in a chimaeric mouse model of temporal arteritis. Aspirin may have a role as a steroid sparing agent in the treatment of GCA[45]. Finally, the observations that thrombocytosis is a potential risk factor for visual loss, that anticardiolipin antibodies may predict disease flares, and the finding of elevated plasma homocysteine levels in patients with active GCA[46], suggest similarities between the mechanistic pathways of GCA and atherosclerosis.

Future Prospects

IL-1α is known to be produced by adventitial macrophages in GCA, and circulating levels are raised in patients with strong systemic inflammatory responses[20]. Inhibition of IL-1α may provide a potential therapeutic target. Mice who are deficient in the interleukin-1 receptor antagonist protein demonstrate transmural inflammation of the elastic arteries at sites of turbulent blood flow, that can be compared to GCA in humans. This appears to be dependent on the presence of an intact IL-1 receptor, suggesting that IL-1 itself mediates the disease process[47]. Therefore, direct inhibition of IL-1 or use of IL-1 receptor antagonist may be of future interest in controlling resistant cases of GCA.

Circulating levels of IL-6 are raised in patients with GCA, and may reflect disease activity. IL-6 inhibition may offer another strategy to combat resistant cases. It has been shown in patients with rheumatoid arthritis that anti-IL6 receptor antibody therapy reduces production of VEGF[48], and given the role of the latter in the formation of new vasa vasorum, this therapy could be of use in GCA. Other potential therapeutic targets may include IFNα, particularly given its central role in regulating macrophage differentiation and cytokine production, and also considering that circulating levels correlate with cranial ischaemic complications.

Conclusion

Alternatives to corticosteroid therapy are warranted in the treatment of GCA. Corticosteroids used over prolonged periods and at high doses have well recognised adverse effects, and in view of this, rapid dose tapering is desirable. In addition, a significant proportion of patients treated with steroids will experience disease relapse. Ensuring good disease control and preventing relapses and is likely to reduce the occurrence of ischaemic complications, such as visual loss and stroke, which are the cause of much unwanted morbidity. Long term corticosteroid requirements may be predicted by monitoring plasma levels of IL-6 and TNFα, and could help to identify those who would benefit from corticosteroid-sparing therapy.

Although there is some evidence for the use of immunosuppressive agents such as Azathioprine and Methotrexate as steroid-sparing agents, further large scale, randomised trials are needed to resolve the conflicts in the current literature, before any firm recommendations can be made with res-

pect to their use in resistant cases.

The use of anti-TNFα agents, such as infliximab and etanercept, although confined to case reports, is interesting and encouraging, but randomised controlled trials are required, in order to confirm their likely benefit, before routine clinical use can be considered.

Finally, given the possibility of a shared common pathway between GCA and atherosclerosis, the administration of aspirin to prevent ischaemic complications should be considered. The use of cardioprotective agents, such as statins has not been addressed, but may be a strategy for future trials, given their known additional immunomodulatory effects.

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