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REVIEW ARTICLES

Temporal Arteritis: Treatment Controversies

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Abstract
Introduction: Although giant cell or temporal arteritis represents 5-10% of ischaemic optic neuropathies and is the most common arteritis in people over 60 years old. Currently there is no established treatment with oral glucocorticoids available.
Background: Glucocorticoid (GC) is still the treatment of choice but has to be started without delay in order to prevent neurological or systemic complications. However, we can resort to intravenous treatment in cases where there is loss of sight or other neurological symptoms. In cases refractory to GC or in those in whom we wish to decrease the dose due to adverse effects, individualised treatment with methotrexate or TNF blockers could be indicated. There is insufficient evidence to recommend other treatments, such as azathioprine, dapsone, cyclosporine, cyclophosphamide or imitinib. In patients with vascular risk factors, anti-platelet therapy with ASA should be assessed. Surgical treatment should be considered in selected cases with symptoms due to arterial stenosis.
Conclusions: The corticoids continue to be the treatment of choice in temporal arteritis, however, given the clinical variability of the disease and the special characteristics of this group of patients, usually elderly and with systemic diseases, we believe that individualised treatment with coherent therapeutic guidelines are essential. Currently there is not only treatment with oral glucocorticoids available, although in our patients we can choose to use intravenous mega-doses, anti-platelet treatment, resort to methotrexate or TNF inhibitors in refractory cases, or even consider surgical approaches.

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En la arteritis de la temporal: controversias terapéuticas

Resumen
Introducción: Aunque la arteritis de células gigantes o temporal representa un 5-10% de las neuropatías ópticas isquémicas y es la arteritis más frecuente en las personas mayores de 60 años, aún no existen pautas de tratamiento establecidas.
Desarrollo: El tratamiento con glucocorticoides continúa siendo el de elección y debe iniciarse sin demora en aras de prevenir complicaciones neurológicas o sistémicas. Sin embargo, podemos recurrir a tratamiento intravenoso en casos con pérdida de visión u otros síntomas neurológicos. En casos refractarios a glucocorticoides o en los que deseamos reducir la dosis por la aparición de efectos adversos, el metotrexato y los agentes bloqueadores del factor de necrosis tumoral podrían estar indicados de manera individualizada. De otros tratamientos —como azatioprina, dapsona, ciclosporina, ciclofosfamida o imitinib— no hay evidencias suficientes para recomendarlos. En pacientes con factores de riesgo vascular se debe valorar la antiagregación con ácido acetil salicílico. El tratamiento quirúrgico se debe valorar en casos seleccionados con síntomas debidos a estenosis arteriales.
Conclusiones: El tratamiento de elección de la arteritis de la temporal continúan siendo los corticoides; sin embargo, dada la variabilidad clínica de la enfermedad y las características especiales del grupo de paciente, habitualmente mayores y con enfermedades sistémicas, consideramos fundamental el tratamiento individualizado según unas pautas terapéuticas coherentes. Actualmente no sólo disponemos de tratamiento con corticoides orales, sino que en nuestros pacientes podremos elegir el uso de megadosis intravenosas, antiagregar, en casos refractarios recurrir a metotrexato o inhibidores del factor de necrosis tumoral o incluso valorar aproximaciones intervencionistas.

Introduction

Although giant cell arteritis or temporal arteritis (TA) represents only 5-10% of ischemic optic neuropathies and is the mostly frequently occurring arteritis in people over 60, there are no established guidelines for its treatment.[1] The use of corticoids and their efficiency are well known, but there are doubts about how to begin treatment, how long to maintain it and how to proceed in refractory cases or when side effects appear.[2-4] The search for less toxic Glucocorticoid (GC) regimes is being promoted, as are new GC-sparing treatments that could open up new fields of therapy, but the results so far are unclear. The present article reviews the literature on the different treatments tested and suggests some therapeutic guidelines for patients with temporal arteritis.

Medical Treatment

Glucocorticoids

Although treatment with GC has been the first choice for over half a century, there is currently no standardised, agreed and universally accepted protocol about the initial dose to use, the duration of the treatment or the rate at which the treatment should be decreased. It is not known whether treatment on alternate days, with the aim of minimizing GC toxicity, is advisable, nor is it certain when TA should be considered resistant to treatment with GC.[5]

Glucocorticoids continue to be the first line of treatment due to their ability to relieve symptoms, both neurological and systemic, quickly and to reduce the acute mortality of vasculitis.[6] They have proved their efficacy in reducing vision complications from TA.[7,8] Although little has been written about the evolution of vision complications before the use of steroids, the rate of blindness has decreased from 60% to 7-25% in the last 50 years.[9-11] Almost all series concur on the fact that vision complications generally occur before beginning GC treatment, which has prompted the majority of specialists to employ them without waiting for the results of a biopsy. The probability of loss of vision is reduced to 1% once GC treatment has begun.[12]

The fact that recovery of vision is rare supports the early start of treatment with GC when faced with clinical suspicion.[4-15] The vast majority of patients with permanent vision loss were subject to delays in diagnosis and treatment.[15-17] In patients with vision symptoms, it is advisable to commence treatment immediately with methylprednisolone (1g/day intravenously for 3 consecutive days), although it has not been demonstrated that this is more efficient than oral treatment.

With regard to the initial dose of GC, there have been no controlled trials in this respect given that, for obvious reasons, it would be unethical to carry them out. The usual initial dose of prednisone is 40-60mg/day or the equivalent.[18] Although some authors argue that with lesser doses (20mg/day) or greater doses (80mg/day) it may be possible to achieve results of at least equal or superior therapeutic success, there are no studies that support this practice.[19-21]

The use of initial megadoses would only be justified within a plan for "inducing remission", which should be followed by a plan for "maintaining remission" with low GC doses or a shorter duration of the treatment.[22] The aim would be to achieve a lasting level of remission after GC has been suspended. However, late loss of vision (registered 2 or more weeks after the start of the GC) is exceptional, whether using megadoses or other more conventional doses.[23-25]

With regard to the rate of GC reduction, the initial dose should be maintained for a minimum of 2 weeks and a maximum of 4. Patients with TA show early improvement in their symptoms, even 24-48 hours after beginning the treatment, together with a rapid drop in the acute phase reactants.[26] In cases in which symptoms persist, the diagnosis of TA should be reconsidered, although the literature which prospectively studies the decrease of GC is very scarce. Retrospective studies using no standardised reduction plan showed that the majority of patients required treatment with GC for at least 2 years, and many for even longer than 4 years. The rate of relapse, especially in the first 2 years, varied considerably, between 26% and 90% depending on the series.[26] The ideal would be for the GC decrease to take place in accordance with the activity of the disease, always in an individualised manner and based on both clinical and analytical parameters. It should also be borne in mind that the reactants of the acute phase could occasionally be normal at the beginning of the disease.[27] In standard clinical practice, depending on the symptoms and on the reactants of the acute phase, GC are generally reduced by 10-20% every 2 weeks.

Although the guideline for reducing GC on alternate days has been tested with TA patients, it is not recommended at present, as it has not been possible to prove a reduction in the occurrence of osteoporosis caused by GC and, in a considerable number of patients, the symptoms are worse on the day "off" GC treatment.[27-29]

Steroid-Saving Immunosuppressive Agents (table 1)

Methotrexate

The use of methotrexate (MTX) in TA treatment continues to be controversial. Its use has been based on the fact that MTX has demonstrated its potential therapeutic effect in other types of systemic vasculitis, such as Wegener's[30,31] or even Takayasu[2,3] disease, which share both histological and physiopathological findings with TA.

There are three studies that, while not suitable for comparison with one another,[32-34] show that MTX reduces the number of relapses experienced by patients with TA, as well as total GC exposure.[35,36] However, they do not support the systematic use of MTX as a GC sparer or for disease control in TA.

Given that TA presents a prolonged process with GC requirements varying enormously from one patient to another,[35] it would be advisable for future studies to concentrate on the analysis of greater subgroups, especially those that showed higher GC requirements as chronic treatment for maintenance. Studies should last longer, for at least 3 years, because very few patients are without GC treatment at that stage. The definition of TA remission should be standardised and this should be the final objective of the treatment even if a minimum dose of GC was required.

Other Immunosuppressors that Spare GC

Although there have been trials with different immunosuppressor drugs as possible GC sparers in TA, most of these studies have been very small and have documented a considerable toxicity of the drug.[37-39] Dapsone in doses of 50-100mg/day has shown a slight efficiency in reducing the GC dose in TA.[37-39] A double-blind random trial with azathioprine (AZA) and placebo showed toxicity that led to withdrawal in one third of the patients, and its GC-sparing effect could be demonstrated only belatedly.[40] Experience with cyclosporine and cyclophosphamide has been scarce and their use is definitely not advised for this population due to their high levels of toxicity.[41,42]

Biological Drugs (table 1)

Tumoral Necrosis Factor Blockers

The biological plausibility of obtaining a therapeutic benefit in TA by means of tumour necrosis factor (TNF) blocking therapy is based on the presence of granulomatous

Table 1 Studies on immunomodulatory treatment of temporal arteritis

Drug	Type of study	Patients, n	Dose	Results	Reference
Methotrexate	Clinical	21	7.5 mg/ week	NS	32
	DB, RA, PC	42	10 mg/ week	Efficient	33
	DB, RA, PC	98	15 mg/ week	NS	34
Infliximab	IC	4	3 mg/ kg	Efficient	47
	IC	2	3 mg/ kg	Not efficient	48
	DB, RA, PC	44	5 mg/ kg	NS	49
Etanercept	IC	1	25 mg, twice/ week	Efficient	50
	DB, RA, PC	8	25 mg, twice/ week	NS	51

DB: double-blind; IC: isolated cases; NS: not significant; PC: versus placebo; RA: Randomized.

inflammation in the temporal artery.[43,44] These findings can be superimposed on those observed in other conditions in which the selective TNF blocking produced very good results.[45] Moreover, an increase in TNF expression[43,44] was noted in immunohistochemical studies of arteries inflamed by TA. It has also been observed that the high TNF production in TA is related to the need for a more prolonged use of GC and a relapse process of vasculitis.[46]

The first results obtained with these biological agents came from small series or isolated clinical cases. Infliximab (a monoclonal anti-TNF antibody) has been used in series of patients with acceptable results.[47,48] However, random double-blind studies have not shown efficiency superior to that of placebo either in reducing the proportion of patients who suffered a relapse or in reducing the percentage of patients whose GC dose could be reduced.[49] Etanercept was able to reduce the dose of GC to alternate days in one patient, but there are no significant results that support the use of this drug.[50,51]

Tumour necrosis factor blocking agents could be suitable for individual patients resistant to treatment with GC. However, their efficacy would be less in non-relapsing TA, in which TNF appears to play a less significant physiopathological role.[46]

Antiaggregation with Acetylsalicylic Acid

The rate of morbidity-mortality in TA is considerably increased by its cerebral ischemic complications.[51] Furthermore, these can appear even when GC treatment with has been started early. The use of acetylsalicylic acid has proven to be effective in reducing cardiovascular mortality and acute cerebrovascular accidents.[52-54] Acetylsalicylic acid appears to have an anti-inflammatory effect on the inflamed blood vessels, through the inhibition of interferon (IFN) gamma, an important T lymphocyte proinflammatory cytokine that is a key element in TA physiopathology.[55] This cytokine is present in high concentrations in the arteries affected by TA.[55,56] This inhibitory effect of acetylsalicylic acid could not be reproduced when using Indometacin, a non-steroid anti-inflammatory drug, so the inhibition of cyclooxygenase could be discarded in this experimental model.

Glucocorticoids are very effective when it comes to eliminating the systemic symptoms of TA and the reactants of the acute phase. However, the inflammatory infiltration of the vessel wall persists and is almost unchanged despite prolonged treatment with GC.

The capacity of acetylsalicylic acid to inhibit the production of interferon v (IFNv) (vital in the production of the inflammatory infiltration of the vessel wall) has been demonstrated in experimental studies and. dexamethasone, a powerful GC, acts by inhibiting the transcription of NF-ÎB and the cytokines derived from its expression, interleukin, (IL), 1, 2 and 6, which are also increased in TA.[55] These findings would suggest the existence of a possible synergistic effect when both therapeutic agents were combined.

Even though the event that causes vision loss in TA is more related to intimal hyperplasia than to a thrombotic event, the inhibition of platelet aggregation and the decrease in IFNv production could reduce the thrombotic risk. Moreover, studies have shown a substantial reduction in the appearance of cerebral ischemic events in patients affected by TA who were taking acetylsalicylic acid.[51,57]

Even though new prospective studies which analyse the risks/benefits of acetylsalicylic acid in patients with TA are necessary, it seems reasonable to individualise therapy and to consider the use of antiaggregants in patients with other risk factors.

Imatinib

Imatinib acts by suppressing proinflammatory actions of the platelet growth factor. In TA, vascular remodelling with intimal hyperplasia can be observed as a response to the inflammation. These wall changes can bring about vascular lumen occlusion and tissue ischemia.[58] The ischemic phenomena occur more frequently in areas where blood flow depends on the carotid or on branches of the vertebral arteries.[59] It seems that platelet-derived growth factor is a decisive factor in the development of intimal hyperplasia in patients affected by TA.[60-62] There are currently no studies that recommend the use of Imatinib in patients affected by TA.

Surgical Treatment

Revascularisation of limb arteries through angioplasty, placing a stent or derivative surgery with a bypass are rarely necessary in cases of TA due to the abundant collateral circulation present in this vasculitis. In most cases, the collaterals are sufficient to maintain the viability of the more distal tissues, even though some patients may present muscular claudication before the start of medical treatment and the pulse of long arteries may be absent. Medical treatment achieves the suppression of inflammation, and most symptoms improve with the appearance of collateral circulation, allowing patients to lead a normal life. In a small percentage of cases, revascularisation techniques can be an option, although re-stenosis is frequent in these cases.[63-65]

Recommendations (table 2)

Temporal arteritis is a frequent disease that can leave serious sequelae in a patient. For this reason, an adequate, structured therapeutic pattern must be followed to reduce the possibility of complications as much as possible. Corticoids continue to be the treatment of choice. The most reasonable initial dose is 40-60 mg/day of prednisone or equivalent doses of other steroids. However, in cases where there is a loss of vision or other neurological symptoms, the use of megadoses of steroids with intravenous boluses of methylprednisolone (1g/day for 3 consecutive days) could be useful to induce remission.

As for monitoring, the initial dose should be maintained for 2 to 4 weeks and then progressively reduced on an individualised basis depending on the clinical manifestations and the reactants of the acute phase. Reducing the dose following a pattern of alternate days does not seem advisable.

In cases refractory to steroids or when the dosage needs to be reduced due to the appearance of adverse effects,

Table 2 Recommendations proposed in the treatment of temporal arteritis

Initial dose	Prednisone 40-60mg or equivalent
Loss of vision	Boluses of methylprednisolone 1g 3-5 days
Neurological symptoms	
Induction of remission	
Retinal affectation	Consider photocoagulation
Decrease of dosage	2-4 weeks of 10-20%
Refractory cases	Methotrexate Tumour necrosis factor blockers
Secondary effects of steroids	Methotrexate
Vascular risk factors	Acetylsalicylic acid
Symptomatic arterial stenoses	Intervention radiology/ surgery

MTX is a therapeutic option to be considered. There is insufficient evidence to recommend the use of other immunosuppressors such as azathioprine, dapsone, cyclosporine or cyclophosphamide, and it should be assessed on an individualised basis. There is insufficient evidence to support the use of Imatinib in patients with TA. Tumoral necrosis factor blocking agents could be indicated in specific cases on patients who had developed a resistance to treatment with GC. In patients with vascular risk, antiaggregant treatment with acetylsalicylic acid is an option to be considered. Surgical treatment should also be considered in selected cases when arterial stenosis symptoms are present.

Conclusions

The preferred treatment for TA continues to be corticoids; however, due to the clinical variability of the disease and the special characteristics of the group of patients (most of whom are elderly and suffer from systemic diseases), individualised treatment following some coherent therapeutic patterns is fundamental. At present, oral corticoids are not the only treatment. Our patients can also benefit from the use of intravenous megadoses, antiaggregants and, in refractory cases, methotrexate or TNF blockers can be used or even interventionist approaches may be evaluated.

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