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Review

Biotherapies in large vessel vasculitis

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ABSTRACT

Giant cell arteritis (GCA) and Takayasu's arteritis (TA) are large vessel vasculitis (LVV) and aortic involvement is not uncommon in Behcet's disease (BD) and relapsing polychondritis (RP). Glucocorticosteroids are the mainstay of therapy in LVV. However, a significant proportion of patients have glucocorticoid dependance, serious side effects or refractory disease to steroids and other immunosuppressive treatments such as cyclophosphamide, azathioprine, mycophenolate mofetil and methotrexate. Recent advances in the understanding of the pathogenesis have resulted in the use of biological agents in patients with LVV. Anti-tumor necrosis factor-α drugs seem effective in patients with refractory Takayasu arteritis and vascular BD but have failed to do so in giant cell arteritis. Preliminary reports on the use of the anti-IL6-receptor antibody (tocilizumab), in LVV have been encouraging. The development of new biologic targeted therapies will probably open a promising future for patients with LVV.

Contents

1. Introduction

Giant cell arteritis (GCA), Takayasu's arteritis (TA) and Behcet's disease (BD) are large vessel vasculitis (LVV). Histologically, the presence of granulomatous lesion cell with giant cells is the most common feature of LVV excepting BD. Indeed, in vascular BD, loss of muscle fibers of the media and the internal elastic lamina and lymphocytic inflammatory infiltrate are usually found in the majority of cases. The histological appearance of TA disease may overlap that of GCA. However, there are some useful pathological features to help their distinction: the thickness of the aortic wall is generally greater in TA than in the GCA. GCA is associated with greater inflammation in intima-media, whereas in TA inflammatory lesions and subsequently fibrotic scars are rather mid-adventitial. Finally, granulomas are more compact in TA than in GCA [1, 2]. Aortic involvement is not uncommon in relapsing polychondritis ranging from 1 to 23% of all patients and usually occurs during the course of the disease [3, 4].

The pathogenesis of LVV remains unclear, but includes vessels injury due to products and various cytokines from activated T cells, natural killer cells, and macrophages. Tumor necrosis factor alpha (TNF-α)

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production occurs primarily in macrophages, T cells and natural killer cells and is important in the formation of granuloma in GCA and TA. BD is associated with enhanced TNF alpha expression [5, 6]. TNF alpha gene polymorphism and altered regulation of TNF alpha expression have been demonstrated in patients with this disorder [7, 8]. Furthermore, serum interleukin (IL)-6 level has been correlated with disease activity in TA [9]. In animal models, deficient mice in interferon regulatory factor 4 (IRF-4)-binding protein, a protein that inhibits IL-17 A production by controlling the activity of IRF-4 transcription factor, rapidly developed a large-vessel vasculitis due to an inappropriate synthesis of IL-17 A.

Glucocorticosteroid (GC) is an effective first line agent but with frequent side effects [10].

Long-term corticosteroid use may be deleterious in LVV. Depending on the series, 20–50% of patients develop side effects associated with corticosteroids, including cataracts, peripheral edema, myopathy, fractures, infection and diabetes. Relapses during the tailing of corticosteroids are frequently described, occurring in 30–40% of cases [11].

Concomitant immunosuppressive therapies allow reduction in steroid dose, but relapses are frequent when GC is discontinued [12].

The objective of this systematic review was to analyze the efficacy and safety of biological agents in patients with LVV (GCA, TA, vascular BD, relapsing polychondritis). Biological agents included anti-TNF alpha agents: infliximab (IFX), etanercept (ETN), adalimumab (ADA) and anti-interleukin 6: tocilizumab (TCZ).

We analyzed 45 articles from the literature (247 patients) including 2 prospective studies, 1 open label trial, 7 retrospective studies, 12 case series and 23 case reports.

2. Results

2.1. Giant cell arteritis

Glucocorticosteroids are the treatment of choice for GCA. Adequate doses quickly suppress clinical manifestations of this disorder and prevent most further ischaemic complications. An initial dose of 40–60 mg per day of prednisone (or equivalent) is recommended [13]. The initial dose of glucocorticosteroids is usually given for 2–4 weeks until all reversible signs and symptoms have resolved and acute phase reactants are back to normal. Then, the dose can be gradually reduced each week or every 2 weeks by a maximum of 10% of the total daily dose. The necessary duration of GC therapy is variable, but in most cases it can be discontinued within 1–2 years. Some patients have a chronic relapsing course and might need low doses of GC for several years [14, 15, 16]. Even with gradual reduction of doses of GC, clinical flares have been reported to occur in more than 50% of patients, particularly during the first 12–16 months, when the prednisone dose is reduced to about 5–10 mg per day [16, 17]. Adverse events related to GC are common, and are related to the age of patients and the cumulative dose of GC. In a population based study [16], 86% of patients with giant-cell arteritis had adverse events including bone fractures, avascular necrosis of the hip, diabetes mellitus, infections, gastrointestinal bleeding, cataract, and hypertensions.

Fourteen articles [18–31] reported 59 GCA patients (32 with polymyalgia rheumatica and 32 with aortitis) receiving TCZ at the dose of 8 mg/kg/month except for 4 patients who received 4 mg/kg/month (Table 1). Most of them were females. Patient ages range from 53 to 79 years. These patients received TCZ because 32 of them were GC dependent, 2 had GC side effects, one was GC resistant. In Loricera et al. [19], (22 GCA patients), TCZ was given due to the lack of efficacy and/or unacceptable adverse events related to previous therapy. In 2 patients, TCZ was used as first line of treatment. Besides corticosteroids and before TCZ therapy, several patients had received immunosuppressive agents including: methotrexate (MTX) (n = 41), azathioprine (AZA) (n = 4), cyclophosphamide (CYC) (n = 4), IFX (n = 4), ETN (n = 3), mycophenolate mofetil (MMF) (n = 2), leflunomide (LFN) (n = 2), rituximab (RTX) (n = 1), abatacept (n = 1), and ADA (n = 1). The median daily prednisone dosage before and after TCZ was 20 mg/day (range 0–70) and 2.5 mg/day (range 0–45), respectively. The CRP level dropped from 30 mg/L (range 0–280) to 1 mg/L (range 0–54). Fifty three of the 59 GCA patients experienced improvement of clinical manifestations. The GC dose has been decreased in 40 patients and stopped in 13 patients. The median time of achieve clinical response delay was of 1 month. The median follow up period was 7 months (range 3–45). Two relapse were reported. Two months after last stopping TCZ, one patient worsened with fever and night sweats reminiscent of the clinical presentation at diagnosis. Another patient, after TCZ withdrawal, at 11 month follow up, described widespread aches and pains, ESR rose to 84 mm/first hour and CRP rose to 37 mg/L. Three deaths were reported. One patient died after the second infusion of TCZ due to a stroke in the setting of an infectious endocarditis. One patient died after three infusions, because of a septicemia. Another patient died of a myocardial infarction after 6 months of treatment.

Recently, a monocentric placebo controlled trial (ACR, San Francisco 2015), not yet published, of TCZ (8 mg/kg/month) in 30 GCA patients (70%–80% newly diagnosed 30%–20% relapsing), was conducted to evaluate the efficacy and the safety of this biological agent. The GC decrease was conducted according to a predefined protocol. After 12 weeks, a complete remission was reported in 17 of the 20 patients who received TCZ (85%) and in 4 of the 10 patients who received the placebo (40%). The difference was statistically significant (p = 0.03). Relapse-free survival was achieved in 17 TCZ-treated and 2 placebo-treated patients by week 52 (p = 0.008). Five adverse effects were reported of whom, 2 osteoporotic fractures in the placebo group and 3 gastrointestinal in the TCZ group.

The GiACTA trial is an ongoing multicenter, randomized, double blind, and placebo controlled study designed to test the ability of TCZ to maintain disease remission in patients with giant cell arteritis. Approximately 100 centers will enroll 250 patients with active disease. The trial consists of a 52 week blinded treatment phase followed by 104 weeks of open label extension [32].

A multicentric, double blinded, randomized placebo controlled trial, not yet published, of abatacept in 49 GCA patients was conducted to evaluate the efficacy and safety of this treatment (ACR, San Francisco 2015). In this study, all the patients had the treatment in phase 1 and only responder patients were randomized in phase 2. Most of patients were responder in phase 1 (84%). For the primary outcome, at 12 months, 48% of patients in the abatacept group were in remission versus 31% the placebo group (p = 0.049). The median duration of remission was 9.9 months in the abatacept group versus 3.9 months in the placebo group. The tolerance was similar in the two groups.

The results of three randomized controlled trials show that anti-TNF agents are not effective in inducing remission or in reducing corticosteroid doses in patients with GCA. A randomized double blind placebo controlled trial of ETN in 17 GCA patients was conducted. After 12 months, 50% of patients in the ETN group and 22.2% in the placebo group were able to control the disease without corticosteroid therapy, p value was not significant [33]. A multicenter randomized controlled trial in 70 GCA patients evaluated the effect of adding a 10 week treatment of ADA to a standardized treatment with GC. ADA did not increase the number of patients in remission on less than 0.1 mg/kg of GC at 6 months [34]. A randomized trial evaluated the efficacy of IFX in 44 GCA patients. IFX did not increase the proportion of patients without relapse, nor did it increase the proportion of patients whose GC dosage was tapered to 10 mg/day without relapse [35].

2.2. Takayasu arteritis

As in GCA, GC is still the mainstay of treatment for TA. However, although most patients initially achieve disease remission, relapses and GC dependence is seen in more than two thirds of patients: between

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