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Review

# Biotherapies in large vessel vasculitis

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ABSTRACT

The mainstay of therapy of large vessel vasculitides (LVV) remains glucocorticoids (GC). Although most patients initially achieve disease remission, relapses and GC dependence are seen in more than two-thirds of cases. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) showed little or no steroid sparing effects, while biological agents represent a valid therapeutic option in patients with severe and/or relapsing LVV.



## 1. Introduction

Glucocorticoids (GC) are the mainstay of treatment in large vessel vasculitides (LVV), but in patients with relapsing-remitting disease, biological agents may represent a valid therapeutic option. Interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) are highly expressed in the inflamed arteries tissues; their serum concentration is higher in the subgroup of patients with strong acute-phase response and higher corticosteroids requirements. Recent data showed that disturbances of B cell homeostasis are also critical in LVV patients. All these data support the rationale of the use of anti-TNFα, anti-IL-6 and anti-CD20 biological agents in LVV. Herein, we summarized the main evidence regarding the use of biological agents in large vessel vasculitis.

## 2. Anti-TNFα

### 2.1. Giant cell arteritis

The mainstay of therapy of newly diagnosed giant cell arteritis (GCA) remains glucocorticoids (GC). Only three randomized clinical trials (RCT) investigated the efficacy of anti-TNFα agents in GCA, two enrolling patients with newly diagnosed GCA [1,2], the third one enrolling patients with longstanding GCA [3].

The first RCT [1] was conducted in 44 patients newly diagnosed GCA after GC-induced remission. Sixteen of these patients were randomly assigned to receive GC plus placebo and 28 patients to GC plus intravenous infliximab (IFX) at a dose of 5 mg/kg of body weight at weeks 0, 2, and 6 and every 8 weeks thereafter. At week 22, IFX therapy did not increase the proportion of patients without relapse compared with placebo, nor did it increase the proportion of patients whose GC was tapered to 10 mg/day without relapse [1].

The second study [2] investigated the effect of adding to standard treatment with GC a 10-week treatment of adalimumab (ADA) (40 mg every other week) in 70 patients with newly diagnosed GCA. The primary endpoint (the percentage of patients in remission on less than 0.1 mg/kg of prednisone at week 26) was not achieved [2].

The third study [3] evaluated the role of TNFα blockade in longstanding GCA: the study was conducted in a population of 17 patients requiring a prednisone dose > 10 mg/day and with a least one GC-related adverse event, randomized to group A, etanercept (ETA) plus GC or group B, placebo plus GC. At 12 months, 50% of patients in ETA group and 22% of those in the placebo group were able to adequately control disease activity without GC therapy, but the between-group difference was not significant [3]. However, patients in the ETA group had a significant lower cumulative prednisone dose during the first year of treatment.

Taken together, these results suggest that TNFα blockers are ineffective or can have only a marginal beneficial effect in newly diagnosed GCA, although the limited number of patients included does not allow to draw definitive conclusions. In contrast, in addition the RCT mentioned above, one open pilot study and case reports have shown efficacy of anti-TNFα drugs in reducing GC requirements in GCA patients with longstanding, relapsing disease [4–6]. This suggests that TNFα inhibitors may have a role in relapsing and/or refractory GCA.

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**Table 1**
Summary of case series using biological agents in GCA[c].

| Study | Biological agent | Number of patients | Median age (range [y]) | Female proportion | Median disease duration (mo, [range]) | Remission rate | Median CRP | | Median prednisone (mg/d) | | Pts w/o prednisone in remission | Relapse rate | Median follow-up period |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Before | After | Before | After | | | |
| Beyer et al., 2011 [23][a,b] | TCZ | 3 | 72 (71–79) | 2/3 | NR | 3/3 | 34.9 | < 4 | 30 | < 7.5 | 0/3 | 0/3 | 6 |
| Sciascia et al., 2011 [20] | TCZ | 2 | 76.5 (76–77) | 2/2 | NR | 2/2 | NR | NR | 25 | 5 | 0/2 | 0/2 | 7 |
| Seitz et al., 2011 [21][a] | TCZ (2 monoRx) | 5 | 71 (63–79) | 3/5 | 6 (3–56) | 5/5 | 14 | < 3 | 20 | 5 | 3/5 | 0/5 | 8.3 |
| Salvarani et al., 2012 [22][a,b] | TCZ (1 monoRx) | 2 | 59 (54–64) | 0/2 | 19 (2, 36) | 2/2 | 51 | 0.4 | 12.5 | 1.25 | 1/2 | 1/2 | 9.5 |
| Unizony et al., 2012 [25][b] | TCZ | 7 | 69 (60–83) | NR | NR (10–24) | 7/7 | 34 | 0.7 | 15 | 0.5 | 4/7 | 2/7 | 7 |
| Cantini et al., 2001 [4][b] | IFX | 4 | 74 (72–75) | 3/4 | 47.5 (42–54) | 3/4 | 46 | 3 | 12.5 | 0 | 3/4 | 0/3 | 5 |
| Andonopoulos et al., 2003 [5] | IFX | 2 | 82.5 (80–85) | 0/2 | NR | 2/2 | 51 | 0.4 | 0 | 0 | 1/2 | 2/2 | 4.5 |

Three studies (Seitz et al., 2011 [21], Salvarani et al., 2012 [22] and Unizony et al., 2012 [25]) also appear in Table 2 with TAK patients.
GCA: giant cell arteritis; TCZ: tocilizumab; monoRx: monotherapy; IFX: infliximab; CRP: C-reactive protein; NR: not reported; TAK: Takayasu arteritis; F/U: follow-up; mo: month; y: year.
[a] In these studies, remission was defined using clinical, biochemical and the absence of new radiographic findings.
[b] In these studies, F/U was 6 mo while patients were in remission.
[c] Reproduced from Osman et al. [43].