Biologics in vasculitides: Where do we stand, where do we go from now?

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Summary

Biological agents represent a valid therapeutic option in patients with severe and/or relapsing vasculitis. Over the last years, some of these agents have become an established therapy (such as RTX in AAV or IFX for ocular BD), and some appear to hold promise to become so. In addition, there are a number of drugs in the pipeline that may contribute to further improve the prognosis of vasculitis. As the range of medications available for vasculitis widens, the need will also increase to define the best treatment schemes as well as to identify those patients that may benefit most from biological agents.

Vasculitides are a heterogeneous group of diseases characterized by inflammation of the vessel wall. The prognosis of vasculitis is variable, but as a rule, an aggressive treatment is warranted in the majority of patients. The number of medications available to treat vasculitis has been on the rise over the last years, with biological agents being now a key part of our therapeutic tools. In this article, we aimed to review the main advances in biological therapy of vasculitis over the last five years.

Large vessel vasculitides: giant cell arteritis and Takayasu arteritis

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are the most common forms of large-vessel vasculitis (LVV). The mainstay of treatment for LVV remain glucocorticoids (GC) [1–3], but relapses during GC tapering and recurrences after GC discontinuation are common, thus requiring prolonged GC treatment with ensuing GC-related adverse events [4]. The results of treatment trials with conventional immunosuppressive agents have overall been disappointing in that no reduction in

¹ The first two authors have equally contributed to the manuscript.
Giant cell arteritis

Two randomized controlled trials (RCT) have failed to prove the efficacy of anti-TNF-α agents in patients with newly diagnosed GCA. In the first trial, Hoffman et al. randomly assigned 16 newly diagnosed GCA patients to receive GC plus placebo and 28 patients to GC plus infliximab (IFX) at a dose of 5 mg/kg of body weight at weeks 0, 2, and 6 and every 8 weeks thereafter. Primary endpoints were the number of patients who remained free of relapse through week 22 and adverse events. IFX therapy did not increase the proportion of patients whose GC dosages were tapered to 10 mg/day without relapse [7]. In a second more recent trial, Seror et al. evaluated the effect of adding a 10-week treatment of adalimumab (ADA) (40 mg every other week) to a standardized treatment with GC on the ability to taper more rapidly the GC doses in 70 patients with newly diagnosed GCA. The primary endpoint (percentage of patients in remission on less than 0.1 mg/kg of prednisone at week 26) was not achieved [8]. A third small RCT evaluated the efficacy of etanercept (ETA) 25 mg twice weekly (n = 8) compared to placebo (n = 9) over 1 year together with GC in 17 biopsy-proven relapsing GCA patients with GC-induced adverse effects. Primary outcome was the ability to withdraw GC and control of disease activity at 12 months. After 12 months, there was no difference in the proportion of patients able to control the disease without GC. Patients in the ETA group had a significant lower cumulative prednisone dose during the first year of treatment, but there were no differences in GC-induced adverse events [9]. Taken together, these results strongly suggest that TNF-α blockers are ineffective or at best have only a marginal beneficial effect in new-onset GCA. In contrast, data from one open pilot study and case reports have reported efficacy of anti-TNF-α drugs in reducing GC requirements in GCA patients with longstanding, relapsing disease [10-12]. This suggests that TNF-α inhibitors may have a role in refractory GCA.

In GCA patients, IL-6 is upregulated within the inflamed arteries and in the peripheral circulation [13-15]. Furthermore, serum IL-6 levels mirror the activity of the disease, and decline with effective GC therapy, suggesting a potential therapeutic role for the IL-6 receptor inhibitor monoclonal antibody tocilizumab (TCZ) [16]. Case reports and small case series have shown the efficacy of TCZ in the treatment of patients with relapsing/refractory GCA [17-24]. A smaller number of newly diagnosed GCA patients naive to GC and other immunosuppressive agents has also successfully been treated with TCZ monotherapy [18,25]. Two patients received TCZ at 4 mg/kg [22], but the majority was infused with 8 mg/kg every 4 weeks. TCZ appeared to improve clinical symptoms, acute-phase reactants, and vascular imaging findings, although the effect on vascular wall inflammation as assessed histologically is still unclear (autopsy data from a GCA patient in clinical remission on TCZ revealed ongoing inflammatory infiltrates in the large vessels) [22]. Another caveat about TCZ therapy is that, so far, only few patients with GCA-related cranial manifestations have received this therapy, raising the question whether TCZ can prevent GCA-related ischemic events. Finally, some patients with refractory GCA who showed an adequate response to TCZ relapsed after its discontinuation, suggesting that long-term therapy may be required, at least in some patients [26]. We have used TCZ in GCA patients with large-vessel involvement with mostly encouraging results, but some patients relapsed after a 6-month treatment period despite switching to MTX maintenance therapy [17]. Ultimately, RCT are required to define the precise role of TCZ in GCA. In this regard, the GiACTA trial (a phase III, multicenter, randomized, double-blind placebo-controlled study to assess the efficacy and safety of tocilizumab in subjects with giant cell arteritis, ClinicalTrials.gov Identifier NCT01791153), is ongoing [27]. It is the largest RCT in GCA to date, aiming to recruit 250 patients over 100 centers worldwide. It is expected that the results will be available in a few years’ time.

Takayasu arteritis

As in GCA, GC are still the mainstay of treatment for TAK [1]. However, although most patients initially attain disease remission, relapses and GC dependence are seen in more than two-thirds of patients [26]. Between 46 and 84% of patients will require a second agent to achieve sustained remission with acceptable GC dosages [28]. In TAK, no RCT are available so far. Conventional immunosuppressive drugs (MTX, AZA, and mycophenolate mofetil [MMF]) have shown limited GC-sparing effects in uncontrolled series, and relapses remain common when the dose of GC is tapered [29-32]. Retrospective open-label studies suggest that anti-TNF-α, in particular IFX, might have a role in the treatment of refractory TAK [33-35]. To date, 120 TAK patients treated with anti-TNF-α agents have been reported [36]. Overall, these findings provide observational evidence that anti-TNF-α blockers are effective and safe in inducing remission in the majority (70–90%) of TAK patients who have been unable to achieve or maintain remission with GC and synthetic immunosuppressors alone. IFX (5 mg/kg of body weight at weeks 0, 2, and 6 and every 8 weeks thereafter), often associated with MTX, is the most commonly used agent (109 IFX, 17 ETA, 9 ADA). Between one third to one half of patients are able to reduce and discontinue GC, but relapses occur in about 40% of patients, requiring an increase in dose or a reduction in dosing intervals, or else a switch to another anti-TNF-α agent [36,37]. These data provide circumstantial evidence in favor of the use of anti-TNF-α agents in
relapsing disease, albeit there is a need of RCT to properly gauge the efficacy of anti-TNF-α therapy in TAK. Similarly to GCA, IL-6 plays a key role in the pathogenesis of TAK. Expression of IL-6 has been detected in aortic tissue samples from TAK patients, and serum IL-6 levels correlate with disease activity, suggesting a potential therapeutic role for TCZ [38-40]. Case reports and small case series have shown efficacy and safety of TCZ in the treatment of patients with relapsing/refractory TAK (to date approximately 20 cases) [17,18,22,41]. TCZ, at a dose of 8 mg/kg every 4 weeks, appears to be very effective for treating difficult-to-control TAK patients refractory to both non-biologic immunosuppressive agents and anti-TNF-α agents. A clinical response allowing taper of GC has been observed and follow-up imaging parameters have also improved in most patients [36]. Newly diagnosed TAK patients naive to GC and other immunosuppressive agents have also been demonstrated to respond well to TCZ monotherapy [17,22]. Again, the effect of TCZ on vascular inflammation is still unclear, and worsening of vascular lesions on imaging despite a favorable clinical and laboratory response has been reported, although infrequently [42]. Because TCZ suppresses serum inflammatory markers (which are strongly IL-6-dependent) even in the absence of a significant clinical response [47], assessment of disease activity in TAK patients on TCZ should preferentially rely on a combination of clinical assessments and serial imaging studies. Large RCT are required to generate convincing evidence of efficacy for both anti-TNF-α and anti-IL-6 (-receptor) therapies.

Increasing evidence supports a role for B cells in the pathogenesis of TAK. Immunohistochemical analyses of aortic wall samples from patients with TA have shown that, in addition to T cells, B cells are among the most prominent cells in the inflamed arterial adventitia [48]. Further, circulating plasmablasts and memory B cells are increased, while naive B cells are decreased in patients with active TAK as compared with inactive and control patients [49]. These findings suggest a potential role for B cell depleting therapy in TAK. There are few reports of patients with active TAK, all refractory to previous therapy with multiple immunosuppressive agents, including anti-TNF-α agents, that have successfully been treated with RTX according to the protocol established for rheumatoid arthritis (1 g at day 0 and 15) [49,50]. However, although RTX may hold promise for treating refractory TAK, the experience available is as yet limited and the duration of follow-up remains short. Prospective studies including larger numbers of patients with longer follow-up are thus needed.

Finally, a trial (abatacept for treating adults with giant cell arteritis and Takayasu’s arteritis, ClinicalTrials.gov Identifier NCT00556439) testing the efficacy of abatacept in LTV recently closed. Abatacept is a protein composed of the Fc region of the immunoglobin IgG1 fused to the extracellular domain of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which prevents T cell activation. In this study, all participants received abatacept and prednisone with a tapering scheme for the first 3 months. At month 3, those participants that had achieved remission were randomly assigned to receive monthly infusions of either abatacept or placebo. The primary outcome of the study is remission duration and the secondary main outcome is drug safety. The results of this study are awaited in a few years’ time.

**ANCA-associated vasculitis**

*Rituximab*

RTX has recently been investigated in both open and controlled trials in patients with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) with interesting results. In 2010 two RCT, RTX versus cyclophosphamide (CYC) for ANCA-associated vasculitis (RAVE) [51] and RTX versus CYC in ANCA-associated renal vasculitis (RITUXVAS) [52], showed that RTX was not inferior to CYC for the induction of remission in patients with ANCA-positive granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), and that RTX might be superior to CYC in patients with relapsing disease [51]. Severe adverse events were similar in both studies [51,52]. The RAVE and RITUXVAS studies had overall similar designs, comparing RTX (375 mg/m² intravenous weekly for 4 weeks) with placebo given as add-ons to GC with a tapering scheme. Patients were only included if they had positive serum ANCA. However, in the RITUXVAS study patients also received two pulses of CYC at onset, while in the RAVE study (where no CYC was used) patients with severe renal failure (defined as creatinine over 4 mg/dL) and severe respiratory failure (defined as requiring mechanical ventilation) were excluded. Therefore, it remains to establish whether RTX is effective in patients with severe renal and respiratory failure due to AAV. Furthermore, in the RAVE and RITUXVAS studies no subgroup analysis was performed to establish the efficacy of RTX in patients with predominantly granulomatous disease (such as orbital masses) versus those with prevalent vasculitic manifestations (such as glomerulonephritis). Because GPA-related orbital tumors, ear-noise-throat manifestations, tracheal and bronchial stenoses, and pachymeningitis are felt to be less amenable to treatment with RTX [53], such manifestations should be probably better treated with CYC or MTX [54]. Finally, because both the RAVE and the RITUXVAS trials excluded patients who did not have measurable serum ANCA as well as those with eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome), their results cannot be generalized to patients who have negative ANCA and/or EGPA. However, limited observational data have shown that RTX can be effective in patients with EGPA refractory to standard therapy, especially when they are ANCA positive [55-60] as well as in patients with AAV but no measurable ANCA titers in the serum [61].
The 18-month results of the RAVE trial have confirmed similar outcomes in the group receiving a single course of RTX (at the dose of 375 mg/m² of body-surface area per week for 4 weeks) relative to the group receiving CYC for induction (at the dose of 2 mg/kg/day administered for 3 to 6 months) followed by azathioprine 2 mg/kg/day for 12 to 15 months for maintenance of remission [62]. Fifty to sixty percent of these patients experienced a relapse over a median time of 11.5 months [63-67]; however, upon re-treatment, RTX effectively induced further remission. Interestingly, data from a retrospective multicenter study of 65 sequential patients receiving RTX for refractory AAV showed that with a strategy of “preemptive” re-treatment of 1 g every 6 months (in the absence of symptoms or reappearance of circulating B cells) no relapses occurred [63].

Other retrospective studies [68,69] explored the use of RTX as a maintenance therapy for AAV with a fixed dose every 4 to 6 months, showing consistent reduction in relapse rates and more prolonged remission over the subsequent follow-up. The French Vasculitis Study Group conducted a RCT named MAINRITSAN (RTX versus AZA for maintenance in AAV) to compare the efficacy of RTX and AZA in the maintenance of AAV remission [70]. Once remission was obtained with a conventional regimen, 115 patients were randomized to receive either (57 patients) a 500 mg RTX infusion on day 1, 15, 5.5 months later, and then every 6 months for a total of 5 infusions over 18 months, or AZA (58 patients) at the dose of 2 mg/kg/day. At month 28, major relapses had occurred in 17 patients of the AZA group (29%) and in 3 patients of the RTX group (5%) [70]. Severe adverse events were similar in both groups (25 in AZA group and 26 in RTX group); two patients in the AZA group died during the study, one after a major relapse and one because of pancreatic cancer.

To understand which patients are at high risk for relapse and when to re-treat remain a challenge in the treatment of AAV. The results of a long-term follow-up RCT showed that patients with positive proteinase 3 (PR3)-ANCA and/or relapsing disease at baseline had the highest risk of relapse, consistent with previously published data [71-73]. Relapses were significantly less in high-risk patients treated with RTX compared with those receiving conventional therapy. Neither B cell counts nor ANCA titers alone predict relapses, but the risk of relapse was very low when both B cell counts and ANCA titers were undetectable [62]. These data raise many questions about the best approach in the maintenance therapy. In particular, it is unclear if in patients at lower risk (patients with anti-MPO positive-MPA) a maintenance therapy in the absence of relapses is desirable, and if high-risk patients (patients with GPA who are anti-PR3 positive) it is better to repeat infusion at fixed times or only upon clinical and/or laboratory relapses. In this regard, an ongoing randomized trial (MAINRITSAN 2) is comparing two different RTX administration therapy strategies. In one arm, patients will receive the same RTX regimen as in the MAINRITSAN study, while in the second arm, patients will receive the infusion only if the CD19 count is > 0/mm³ or the ANCA titer becomes positive or raises [54]. A recent retrospective study of 53 patients showed that relapses occurred after reconstitution of B cells, accompanied or preceded by an increase in ANCA levels [74]. Future data will help to clarify whether re-treatment decisions could be individualized based on factors such as serial B cell count and PR3 ANCA titer. On the other hand, if one pumps for a fixed regimen scheme, it is unclear whether RTX should be prescribed as maintenance therapy at doses of half or 1 gram every 6 months. A concern of long-term RTX treatment is the risk of serious infections [75]. However, it is unclear whether prolonged therapy with RTX is per se a risk factor for infections. At present, hypogammaglobulinemia and a low CD4 count have been linked to an increased risk for infections in RTX-treated patients [76], whereas in another study, the rate of serious infections was similar in patients with mild, moderate, and severe hypogammaglobulinemia [77]. Recently, the French Vasculitis Study Group has issued recommendations regarding the use of RTX in AAV [54,78]. According to the authors, RTX should be preferred over CYC for relapsing patients, for women of childbearing age, and for patients who have received a cumulative CYC dose in excess of 10 g, while the use of RTX is discouraged for patients with mild or limited disease and those with predominantly granulomatous lesions.

Anti-TNF-α agents

The only anti-TNF-α agent that appears to have a role in AAV is IFX. In a prospective RCT [79], 17 patients with systemic GPA refractory or intolerant to GC and other immunosuppressants (including oral CYC) were randomly assigned to receive IFX or RTX. The remission rates were similar in both groups with a trend favoring RTX, but during long-term follow-up RTX was significantly better in achieving and maintaining remission [79]. The Wegener’s Granulomatosis ETA Trial (WGET) compared ETA with placebo ad adjunctive treatment to standard therapy with CYC or MTX. This trial showed that ETA was not effective for the maintenance of remission in patients with GPA; in addition, there was a high rate of treatment-related complications in the group taking ETA plus CYC or MTX including a higher-than-expected incidence of tumors [80]. ADA associated with standard therapy with CYC and GC showed no major benefit in achieving remission in a phase 2, open label, prospective study in patients with renal AAV [81].

Emerging and less common therapies

Abatacept is a ligand-binding domain of CTLA4 plus a modified Fc derived from IgG1 that inhibits T cell activation. In an open label prospective trial of 20 patients with non-severe relapsing GPA, abatacept induced remission in the 80% of cases at a median of 1.9 months and improvement in 90% of cases [82]. Belimumab is an anti-B-cell activating factor (BAFF) agent that targets B cells. The BAFF receptor is expressed in many stages of
the B cell lineage including plasma cells. A RCT on relapse prevention in AAV with belimumab is currently ongoing (BREVAS trial) [83].

Alemtuzumab is a monoclonal anti-CD52 antibody (Campath-1H) able to deplete lymphocytes, macrophages and monocytes. In an open-label trial, 71 patients with refractory or relapsing AAV where treated with alemtuzumab, which induced a sustained remission in 85% of patients [84]; nevertheless, a high rate of relapse was observed. A RCT is required before recommending Campath-1H as treatment for refractory AAV.

In AAV, the C5a complement fragment mediates neutrophil recruitment and activation at sites of inflammation via binding to its receptor C5a-R. A phase 2 RCT has recently been conducted to investigate the potential role of CCX168, an oral specific C5a-R antagonist, in patients with active AAV and renal involvement. CCX168 was added to CYC and low-dose prednisone or (in some patients) to CYC without prednisone. The comparator was standard-of-care therapy, i.e. CYC plus high-dose prednisone tapering. The results showed that CCX168 plus CYC appeared to be at least as effective, if not more effective, as full-dose GC plus CYC in improving renal parameters and inducing remission of renal vasculitis [85].

TCZ was successfully used in a case of a woman with MPO-ANCA pauci-immune glomerulonephritis with necrotizing and crescent formation associated with rheumatoid arthritis [86].

Mepolizumab (MPZ) is a monoclonal anti-interleukin (IL)-5 antibody. In case reports and open-label trials [87-90], MPZ has been used in EGPA patients with relapsing-refractory disease with a non-vasculitic, ANCA-negative pattern, including prevalent asthma and “eosinophilic involvement” (frequent cardiac or pulmonary involvement, excluding pulmonary hemorrhage), low frequency of glomerulonephritis, purpura, and mononeuritis multiplex. In these cases, MPZ showed a GC-sparing effect, but relapses were common upon treatment withdrawal [91].

Adamantiades-Behçet disease

Anti-TNF-α agents

Anti-TNF-α agents are increasingly being employed in patients with Adamantiades-Behçet disease (BD) [92,93]. In a systematic review of 369 often refractory patients, containing retrospective and prospective studies, TNF-α blockers were effective in 90% of patients with mucocutaneous lesions, 89% of patients with ocular involvement, and 91% of those with neurological involvement related to BD [93]. Relapses were common after cessation of treatment, but remission was achieved after retreatment. The monoclonal anti-TNF-α antibody IFX was most commonly used, typically at a dose of 5 mg/kg at 0, 2, 6, weeks and subsequently every 8 weeks. Concomitant use of TNF-α blockers and traditional immunosuppressants such as AZA, MTX or ciclosporin (Cy-A) has been mapped to better outcome in ocular disease than monotherapy with TNF-α blockade [92-94].

There is a double-blind placebo controlled study of 40 patients treated with ETA: the patients enrolled had mostly mucocutaneous lesions, and patients with organ involvement were excluded. ETA was effective in suppressing oral ulcers and nodular lesions, whereas it proved less beneficial for genital ulcers and arthritis [95].

At present, IFX remains the most widely used anti-TNF-α agent in BD [92,93,96], but in case of failure of (or allergy to) IFX, switching to ADA is a reasonable therapeutic option [92,93,96,97]. Specifically, ADA has shown its efficacy in multiple studies, even in case of lack or loss of efficacy of IFX [98-101]. In contrast, mostly indirect evidence from Crohn’s disease [102] and uveitis associated with other rheumatic diseases [103] may suggest that ETA may be less effective in ocular and gastrointestinal manifestations.

In case of vascular involvement (venous or arterial thrombosis and/or arterial aneurysms), very limited published data, the majority of them regarding IFX [104-109] and a few ADA [110], suggest that TNF-α blockers may be effective for these manifestations.

As underlined in the 2009 European League Against Rheumatism (EULAR) [111] recommendations for the management of BD, the response to IFX usually is rapid and efficacious. Therefore, IFX could represent a viable alternative to conventional therapy in refractory cases. In particular, the EULAR suggests that IFX may be used even as first-line therapy in severe ocular disease, i.e. when there is a two-line drop on a 0–10 scale in visual acuity, when there is cystoid macular edema, and in the presence of retinal vasculitis. We have also used IFX in patients with severe neuro-Behçet (both new-onset and relapsing) with favorable responses [112].

Other biological therapies

Anti-IL-1 agents such as anakinra, canakinumab and gevokizumab have been shown to be effective in case of refractory ocular BD [113-116]. Gevokizumab was administered to 7 patients with resistant uveitis and retinal vasculitis in an open label pilot study showing a rapid and sustained reduction in intraocular inflammation and a complete regression within 4-21 days [114].

A RCT (number NCT02258867, EYEGUARD™-US) to evaluate efficacy and safety of gevokizumab in the treatment of BD-related ocular disease is currently ongoing. TCZ has successfully been employed in multiple cases of neuro-BD [117-119] and in one case of ocular BD [120] refractory to traditional and anti-TNF-α therapy. The rationale for the use of TCZ in neuro-BD is the evidence of markedly raised IL-6 levels in the cerebrospinal fluid (CSF) of patients with active neuro-BD. In contrast, CSF levels of TNF-α, interferon-γ, IL-8 and IL-10 were not higher in patients with neuro-BD compared to unaffected controls [118,121,122]. In our case series, however, although all 3 patients treated with TCZ for refractory neuro-BD initially responded well, one patient developed a loss of efficacy over...
time, while in another patient withdrawal of TCZ led to a relapse [119]. Another group has documented that two patients with severe mucocutaneous lesions due to BD that were treated with TCZ did not have a favorable response [123].

RTX showed efficacy in pilot studies of patients with severe ocular involvement resistant to conventional therapy [124,125]. However, the data available is very limited, and in one study, efficacy assessment was performed only 6 months after the onset of RTX therapy [124]. It is thus unclear whether RTX has a clear role in treating BD.

Alemtuzumab was efficacious in case of refractory muco-cutaneous, ocular and/or neurologic involvement [126,127]. In contrast, a double blind control trial did not show benefit of daclizumab, an anti-CD25 antibody, compared to placebo in case of severe ocular BD [128]. The significant leucopoenia that is often observed after alemtuzumab therapy (and which may persist over longer periods) limits the use of this drug to highly refractory patients. Finally, a multicenter, randomized, double-masked, placebo-controlled study (SHIELD study) to assess the safety and efficacy of adjunctive secukinumab, an anti-interleukin-17A antibody, to standard-of-care immunosuppressive therapy in patients with Behçet’s disease with posterior uveitis or panuveitis did not show efficacy in reducing recurrences of ocular symptoms [129].

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References


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