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Chapter

Treatment of Vasculitis: Beyond the Basics

Muhammad Ishaq Ghauri and Muhammad Shariq Mukarram

Abstract

Vasculitis is the inflammation of blood vessels in the human body. It causes changes and remodeling in the walls of the vessels that include thickening, narrowing and scarring. As a result, the blood flow to the organs and tissues gets restricted leading to organ damage. The cause of primary vasculitis is not known; however, most cases are thought to be autoimmune. In the present era, it is getting difficult to treat vasculitis with conventional therapies, which includes cyclophosphamide, methotrexate, azathioprine and mycophenolate mofetil, with increasing rates of relapses. Since ever, corticosteroids and cytotoxic agents or immunosuppressants have been the mainstay for treating systemic vasculitis. However, the introduction of newer biological agents have bring about a revolution in the treatment of relapses and in cases where there is failure to induce and sustain remission.

Keywords: vasculitis, granulomatosis with polyangiitis, ANCA-associated vasculitis, giant cell arteritis, Takayasu arteritis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, anti-TNF alpha, monoclonal antibody, rheumatoid arthritis

1. Introduction

Vasculitis is a group of heterogeneous disorders that are characterized by inflammation, also sometimes necrosis of blood vessels that includes the veins, arteries and capillaries. Several different forms have been identified. The pathophysiology of vasculitis mainly involves the immune system of the body. In large vessel disease, particularly giant cell arteritis, it is a T cell-driven process activating the CD4 T cells which in turn promote the recruitment of macrophages and monocytes to the vessel wall causing vascular injury. This leads to release of various inflammatory markers and cytokines for example, Interleukin 1 and Interleukin 6, causing systemic inflammation [1]. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis involves the activation of neutrophils that release inflammatory cytokines. They also induce formation of neutrophil extracellular traps that are necessary constituent of innate immunity. These neutrophil traps are injurious to small vessels that not only cause vascular injury but also produce antineutrophil cytoplasmic antibody, therefore producing a vicious cycle [2].

The aim of this chapter is to highlight the rising number of therapeutic options available to treat systemic vasculitis. Use of biologics has shown promising results, especially Rituximab and Infliximab while others remain in the pipeline. The recent emergence of these agents, that selectively targets the components of immune system, have brought an insurgence in treatment of systemic vasculitis. In this chapter

we discuss the treatment of vasculitis beyond the prototype drugs (cyclophosphamide, azathioprine, mycophenolate mofetil, etc.), with biological agents.

2. Classification

American College of Rheumatology (ACR) presented the classification criteria for vasculitis in 1990 (**Table 1**). According to this criteria vasculitis was classified into primary and secondary types. Both these types were dependent on the size of vessel involved. Vasculitis affecting the large arteries include giant cell arteritis (GCA) and Takayasu arteritis. Medium vessel vasculitis includes polyarteritis nodosa (PAN) and Kawasaki disease, while small vessel vasculitis contains granulomatosis with polyangiitis (GPA) formerly known as Wegener's granulomatosis (WG), Churg-Strauss syndrome now known as eosinophilic granulomatosis with polyangiitis (EGPS), microscopic polyangiitis (MPA), Henoch Schonlein purpura and cryoglobulinemia. Secondary vasculitides encompass vasculitis secondary to rheumatoid arthritis and various infections (bacterial, viral and fungal) [3].

Infections affecting large arteries commonly include *Staphylococcus*, *Salmonella*, *Streptococcus*, coccidioidomycosis and treponema pallidum. Hepatitis B and C virus along with human immunodeficiency virus and Parvovirus B19 commonly affects medium sized vessels. Possible mechanism for infection related vasculitis includes (a) direct microbial invasion and (b) immune-mediated process either by humoral or cellular responses. Hepatitis B virus has firmly been seen with polyarteritis nodosa for more than 30 years. In France, the declining rate of hepatitis B infection has correlated with falling levels of hepatitis B-associated polyarteritis nodosa. There is a strong association between hepatitis C virus and mixed essential cryoglobulinemia. Vasculitis has been identified as a rare manifestation of human immunodeficiency virus. Multiple patterns have been described including polyarteritis nodosa, hypersensitivity vasculitis and large vessel disease [3].

Course of rheumatoid arthritis can be complicated by medium to small vessel vasculitis. This is common in men and linked with positive RA factor. It may present in a variety of ways including distal arteritis, splinter hemorrhages, peripheral neuropathy with mononeuritis multiplex and aortitis [4].

In year 2012 the International Chapel Hill Consensus conference adopted names for vasculitis on nomenclature of vasculitides as shown in **Table 2**. This classified vasculitis not only according to the size of vessel involved (as in ACR criteria) but also included a few other subtypes mainly, variable vessel vasculitis, single organ vasculitis, vasculitis associated with systemic diseases and vasculitis associated with probable etiology [5].

Dominant vessel	Primary	Secondary
Large arteries	Giant cell arteritis Takayasu arteritis	Aortitis associated with rheumatoid arthritis, infections
Medium arteries	Classic polyarteritis nodosa Kawasaki disease	Hepatitis B-associated, polyarteritis nodosa
Small vessels and medium arteries	Granulomatosis with polyangiitis, Churg-Strauss syndrome, microscopic polyangiitis	Vasculitis secondary to rheumatoid arthritis, drugs
Small vessels	Henoch-Schonlein purpura Cryoglobulinemia	Drugs, hepatitis C associated, infections

Table 1.
ACR classification of vasculitis [3].

Large vessel vasculitis
Takayasu's arteritis
Giant cell arteritis
Medium vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Small vessel vasculitis
Anti-neutrophil cytoplasmic antibody-associated vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Immune complex small vessel vasculitis
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch Schonlein purpura)
Variable vessel vasculitis
Behcet's disease
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Vasculitis associated with probable etiology
Hepatitis C-associated cryoglobulinemic vasculitis
Hepatitis B-associated vasculitis
Drug-associated immune complex vasculitis
Drug-associated ANCA-associated vasculitis

Table 2.
Modern Chapel Hill classification [5].

A wide range of drugs have been reported to cause a vasculitic reaction. ANCA-associated vasculitis has been attributed to use of various drugs including Hydralazine, Propylthiouracil, Allopurinol and Sulfasalazine. Leukotriene receptor antagonist, Montelukast and Zafirlukast, have been linked to Churg-Strauss syndrome. Acute vasculitis may be the presenting feature of an undiagnosed malignancy. Common malignancies associated with vasculitis are myelodysplasia, lymphoma and multiple myeloma [3].

3. Treatment with biological agents

3.1 Rituximab

It is a monoclonal antibody, which is directed against CD20 that is expressed on developing B cell. Although not clearly understood, this antibody can induce apoptosis of these developing B cells. In April 2011, Rituximab was the first agent to be approved by FDA for the treatment of vasculitis [6].

In the Rituximab in ANCA-associated vasculitis (RAVE) trial, patients with GPA and MPA who were being given steroid therapy were randomized and received either oral cyclophosphamide or I/V Rituximab (four infusions). Patients who were given cyclophosphamide were switched to azathioprine after going into remission while those with Rituximab were switched to oral placebo. At the end of 6 months, Rituximab was found to be non-inferior to cyclophosphamide at inducing remission and was found to be superior to cyclophosphamide for patients with relapsing disease [6].

Another study showed single course of Rituximab to be non-inferior to oral cyclophosphamide, which was followed by azathioprine for remission maintenance [7].

In the Rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS) trial, where 44 patients were diagnosed with ANCA-associated vasculitis, patients were randomized to receive Rituximab along with only two infusions of cyclophosphamide. This was compared with patients who were given I/V cyclophosphamide for 3–6 months followed by azathioprine. The rate of sustained remission was similar in both groups [8].

These studies indicate that Rituximab is comparable in efficacy to cyclophosphamide for remission induction. Moreover, Maintenance of remission under Rituximab in systemic ANCA-associated vasculitis (MAINRITSAN) trial 115 patients with either GPA or MPA were given either azathioprine or Rituximab in a dose of 500 mg IV × 2 doses (after achieving remission with cyclophosphamide). At the end of the study, major relapse rate was significantly lower in patients who received Rituximab [9].

Rituximab has also shown remarkable results in patients with EGPA whose disease was refractory to usual treatments (e.g. cyclophosphamide). One of the largest case series showed nine patients with EGPA refractory to conventional therapy, when treated with Rituximab were either in total or partial remission at the end of 3 months [10].

The safety and efficacy of Rituximab has been evaluated by Puechal et al. in patients with active systemic rheumatoid vasculitis (SRV). Out of 17 patients with active SRV who were treated with Rituximab, 12 patients achieved complete remission of their disease at the end of 6 months. The Birmingham Vasculitis Activity Score (BVAS) for rheumatoid arthritis dropped down from a baseline of 9.6 to 0.6 and the daily average dose of Prednisolone declined from 19.2 to 9.7 mg. After a year, 14 patients were in sustained remission [11].

Rituximab works by acting over B cells, clearing them from the body. It is the most extensively studied agent that has proved to be efficacious in most forms of vasculitis, especially ANCA-associated vasculitis. It is now the preferred choice over cyclophosphamide in order to reduce the adverse effect profile. Also, Rituximab is considered a suitable therapeutic option for inducing remission in patients with active vasculitis associated with rheumatoid arthritis.

Table 3 summarizes the clinical outcomes of different trials carried out using Rituximab as treatment for systemic vasculitis.

3.2 Infliximab

This is an IgG1, kappa monoclonal antibody specific for human tumor necrosis factor alpha. TNF alpha possesses multiple pro inflammatory properties for example, induction of Interleukin 1 and Interleukin 6, neutrophil activation etc. According to recent research, Infliximab is in phase 3 clinical development for treatment of Kawasaki disease [12].

Study	Agent	Disease	Outcome
RAVE trial	Rituximab	GPA and MPA	Rituximab was found to be non-inferior to cyclophosphamide at inducing remission and superior to cyclophosphamide for patients with relapsing disease
RITUXVAS trial	Rituximab	ANCA-associated vasculitis	Rate of sustained remission were similar in patients taking Rituximab vs. those given cyclophosphamide alone
MAINRTSAN trial	Rituximab	GPA/MPA	Significantly reduced the relapse rate

Table 3.
Rituximab trials [6, 8, 9].

One clinical trial studied the role of Infliximab in granulomatosis with polyangiitis exclusively. These patients were followed even after the discontinuation of Infliximab to monitor the remission maintenance. The reduction of their Birmingham Vasculitis Activity Score was significant. Surprisingly no severe adverse effects, deaths or infections were noted [13].

Use of TNF alpha inhibitors is not encouraged in giant cell arteritis. In a randomized controlled trial, some newly diagnosed patients with giant cell arteritis were given Infliximab along with corticosteroids (before tapering them). No significant difference was observed in patients who were successfully tapered off corticosteroids. Moreover, few subjects had a higher infection rate with the use of Infliximab [14].

Use of Infliximab has shown great effectiveness in refractory Kawasaki disease [15]. Single-dose Infliximab (5 mg/kg) was given to seven patients who failed to achieve remission with the standard therapy. These patients showed improvement without any adverse effects [16]. In another study, good response was seen in two patients with Kawasaki disease when treated with Infliximab who had a relapse with the conventional therapy [17].

This anti-TNF (tumor necrosis factor) agent has shown promising results in Wegener's granulomatosis in reducing the disease as well as inducing remission. Use of Infliximab is encouraged in medium vessel vasculitis. Patients with Kawasaki disease, who failed to respond to conventional therapy and those who experienced a relapse, reacted well to this agent. Unfortunately its use in giant cell arteritis is not promoted as suggested by a clinical study (as discussed above) in which patients with giant cell arteritis were treated with Infliximab showed no significant response, instead resulted in a higher rate of infection.

Table 4 summarizes the clinical outcomes of different studies and trials showing effectiveness of Infliximab in different types of vasculitis.

Study	Agent	Disease	Outcome
Lamprecht et al.	Infliximab	WG	Decrease in BVAS. No deaths, infections or adverse effects
Randomized trial	Infliximab	GCA	No significant difference. Increased rate of infection
Burns et al.	Infliximab	KD	Improvement in patients who failed to achieve remission by standard therapy/refractory disease

Table 4.
Infliximab trials [13–15].

3.3 Etanercept

This is one of the most rigorously studied agent, which is also a tumor necrosis factor inhibitor. Its role has been studied in GPA and MPA for maintenance of remission. In WGET, 174 patients received methotrexate or cyclophosphamide for their remission and were then randomized to get Etanercept or placebo. Unfortunately, there was no significant difference in rate of sustained remission between Etanercept and placebo [18].

Etanercept (25 mg twice weekly) was given to 20 patients with Wegener's granulomatosis over a period of 6 months, in twice-daily dose. Out of these patients, 70% had never had remission of their disease. This drug was combined with either cyclophosphamide or methotrexate. During the treatment, 80% patients went into disease remission and their Birmingham Vasculitis Activity Score fell significantly. However, three patients experienced major flare despite the therapy [19, 20].

The major drawback is the increased incidence of cancer in patients treated with Etanercept. Six of 92 patients developed a solid tumor. These tumors included mucinous adenocarcinoma of colon, metastatic cholangiocarcinoma, renal cell carcinoma and breast carcinoma [21].

Wegener's granulomatosis itself is also associated with increased risk of malignancy. The specific malignancies associated with it are bladder carcinoma, squamous cell carcinoma, leukemia and lymphomas [22].

Use of these two agents (Infliximab and Etanercept) have shown promising results in Takayasu arteritis as demonstrated by a case series in which 15 patients with treatment resistant disease were treated with either of the drug. After introduction of these agents, the average dose of corticosteroid dropped from 20 mg (range 12.5–40 mg) to 0 mg (range 0–20 mg). Among these 15 patients 93% showed remarkable improvement and 67% experienced steroid free remission for up to 3 years [23].

Etanercept is one of the most widely studied agents, which is also an anti-TNF drug, and has been seen to be beneficial not only in ANCA-associated vasculitis but also in large vessel vasculitis (Takayasu arteritis). The biggest disadvantage of this medication is the higher incidence of different types of cancers.

Table 5 summarizes two trials showing clinical outcomes of Etanercept in patients with Wegener's granulomatosis also known as granulomatosis with polyangiitis.

3.4 Belimumab

This is a human IgG1 gamma monoclonal antibody specific for soluble human B lymphocyte stimulator protein, also known as B cell-activating factor. Surprisingly, this is the only drug in late stage development for microscopic polyangiitis [12].

Currently this agent is in Phase 3 trial. Its efficacy and safety are being tested in a randomized, double blind study in combination with azathioprine. The dose given to patients is 10 mg/kg at days 0, 14, and 28 then after every 28 days till the study ends (clinical trials) [24].

Study	Agent	Disease	Outcome
WGET trial	Etanercept	WG	No significant difference in rate of sustained remission between Etanercept and placebo
Luqmani et al. and Stone et al.	Etanercept	WG	80% patients went into disease remission and their BVAS fell significantly. Three patients developed major flare

Table 5.
Etanercept trials [18–20].

Belimumab is a relatively newer agent that is currently under trial but has shown positive results in treatment of microscopic polyangiitis.

3.5 Mepolizumab

Mepolizumab is an Interleukin 5 humanized monoclonal antibody that binds to free Interleukin 5. It causes arrest of bone marrow eosinophil maturation. This monoclonal antibody is directed against Interleukin 5, which is a cytokine critical for activation of eosinophils. Mepolizumab when administered in a dose of 300 mg subcutaneously every 4 weeks, proved to be effective in prolonging disease remission, reducing the use of steroid [25].

Use of this agent has shown prompt normalization of peripheral eosinophil counts, as well as reduction in glucocorticoid usage. Two studies that showed use of Mepolizumab in EGPA, it led to decreased disease activity, normalization of eosinophil count and reduction of steroid use. However, cessation of this drug resulted in disease flare [26, 27].

Mepolizumab works by halting activation of eosinophils, acting directly on them. This biological agent is recommended in treating Churg-Strauss syndrome, although it is still under various trials. The major drawback is the disease flare caused after discontinuing the medication.

3.6 Tocilizumab

Tocilizumab is a humanized monoclonal antibody that binds to membrane-bound and soluble Interleukin 6 receptors and inhibits Interleukin 6 signaling pathways [28].

A study assessed eight patients who had refractory Takayasu arteritis. Two cases were refractory to Infliximab and three did not reach remission on steroids and methotrexate. Altogether eight patients received Tocilizumab and were followed for 18 months. Of these eight patients, seven achieved remission. This shows that Tocilizumab can be a potential therapy for patients with Takayasu arteritis refractory to anti-TNF alpha therapy [29].

A retrospective study assessed the effectiveness of Tocilizumab in complicated large vessel vasculitis. Patients were treated with Tocilizumab out of which eight had giant cell arteritis, two had large vessel vasculitis associated with rheumatoid arthritis and one had Takayasu arteritis. These patients were followed for 23 months. At the end of duration, seven patients were in remission, one patient relapsed after discontinuing the drug, and one patient suffered from serious infective complication. Two patients died, although cause of death was not attributable to the use of Tocilizumab. Three relapses occurred but remission was regained by switching the usual subcutaneous administration of Tocilizumab to intravenous [30].

Glucocorticoids are the conventional treatment for giant cell arteritis but adverse effects are common, so are the relapses, soon after tapering the steroids. Although the exact cause of death is not known, cytokines such as tumor necrosis factor alpha and Interleukin 6 have been implicated. A retrospective study included 134 patients from 40 different centers who were diagnosed with giant cell arteritis either by temporal artery biopsy or imaging techniques. All these patients had received high dose of steroids in past and majority of patients had been given biologic immunosuppressives such as Abatacept, Infliximab or Rituximab. Tocilizumab was given either intravenously (8 mg/kg 4 weeks apart) or subcutaneously (162 mg/week). At the end of 1 month the ESR and CRP had fallen and percentage of patients with anemia had decreased. Those who were followed for 2 years, amongst them 39 were seen

Study	Agent	Disease	Outcome
Mejla et al.	Tocilizumab	TA	Seven out of eight cases refractory to either Infliximab or methotrexate achieved remission
Toc in large vessel vasculitis (Marc Schmalzing)	Tocilizumab	GCA, RA vasculitis, TA	After follow up of 23 months, seven were in remission, one relapse after stopping the drug, three relapses but regained remission
IL-6 blocker exceeds (Nancy Walsh)	Tocilizumab	GCA	Patients who were on follow up till 2 years, out of them 39 were seen in remission. These patients had already taken biologics including Abatacept, Infliximab and Rituximab

Table 6.
Tocilizumab trials [29–31].

Agent	Mechanism of action	Dosage
Rituximab	Monoclonal antibody directed against CD20	500 mg intravenous
Infliximab	Anti-TNF alpha	5 mg/kg intravenous
Etanercept	Anti-TNF alpha	25 mg intravenous
Belimumab	Monoclonal antibody that inhibits B cell activating factor	10 mg/kg intravenous
Mepolizumab	Monoclonal antibody directed against Interleukin 5	300 mg subcutaneous
Tocilizumab	Monoclonal antibody directed against Interleukin 6	8 mg/kg intravenous 162 mg subcutaneous

Table 7.
Commonly used biological agents in the treatment of systemic vasculitis.

in remission with acute phase reactants within normal limits and minimum steroid dose (0–5 mg/day). However, after an average follow up of 12 months, 32 patients reported an adverse infection because of which 17 patients had to discontinue the therapy [31].

Tocilizumab works against the pro-inflammatory cytokine Interleukin 6 and has proven its efficacy in Takayasu arteritis that has failed to respond to Infliximab. Giant cell arteritis, non responsive to various other biological agents, has reacted remarkably to Tocilizumab by achieving disease remission in most of the cases. Despite all its applauding outcomes, life-threatening infection remains a serious complication.

Table 6 shows outcomes of studies that have evaluated the effectiveness of Tocilizumab in different types of vasculitis.

Table 7 summarizes the commonly used agents to treat systemic vasculitis, as discussed in this chapter, along with its mechanism of action and dosages.

4. Conclusion

In recent times use of high dose corticosteroids, cytotoxic and immunosuppressant drugs has improved the prognosis of systemic vasculitis dramatically. However, some patients still do not respond to conventional therapy or may not achieve remission. Few of them would relapse and a large number of patients develop illness secondary to the adverse effects caused by long term use of these drugs. The advent

of biological agents has not just let to a better understanding of pathophysiology of systemic vasculitis, but has also proved to be safe and efficacious. Among these agents, anti-TNF and anti-B cell therapy have been the first choice in many cases. Although clinical data are still insufficient, these agents seem to occupy most of the market in near future [32].

5. Methods used for research of articles

We collected information by systematic review of the PubMed, scientific abstracts and by searching textbooks of Rheumatology.

Author details

Muhammad Ishaq Ghauri and Muhammad Shariq Mukarram*
Department of Medicine, Jinnah Medical College Hospital, Karachi, Pakistan

*Address all correspondence to: shariq.msm@gmail.com

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