Use of Anti TNF-α Therapy in Systemic Vasculitis

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Abstract

There are several vasculitic disorders still labeled as difficult-to-treat cases. Effective treatment for those patients is warranted to reduce the mortality and morbidity that resulting from these disorders. An extensive review for the literatures that addressed using of anti TNF-alpha in several vasculitic disorders was conducted. Use of anti TNF-alpha agents is a promising modality in several vasculitic disorders. Despite lacking well-conducted randomized controlled trials, more open-label studies are required to examine in-depth the safety and efficacy of those agents.

Keywords: Vasculitic disorders; Systemic vasculitis; TNF α; Macrophages

Background

There are several vasculitic disorders still labeled as difficult-to-treat conditions due to its rarity and complexity at the time of presentation [1]. The need for effective treatment for vasculitis is demanding since it carries a high incidence of morbidity and mortality either as a long term consequence of the disease itself or from the therapeutic interventions [1]. However, the available studies to provide evidence of therapies to practicing clinicians are mostly based on non-randomized controlled trials. Conducting a well-controlled randomized clinical trial is difficult due to multiple limitations; for example, failure to establish a measurable endpoint in vasculitic disorders leads to different endpoints, making it difficult to obtain evidence from these trials [2,3]. Having a statistical power by large number of patients is another limitation due to its rarity [2,3]. Tumor necrosis factor is a pro inflammatory cytokine primarily by iop polysaccharide stimulated macrophages and monocytes [4]. TNF-α plays a crucial role in process of inflammation via several ways which include adhesion molecule expression, pro inflammatory cytokine release and inhibition of regulatory T cells. TNF-α is increasingly considered as a central player in pathophysiology of systemic vasculitis, a targeting therapy to TNF α is the current trend to treat systemic vasculitis [5].

Introduction

The available anti TNF-α agents are Infliximab, Adalimumab, Etanercept, Certolizumab pegol and Golimumab. Infliximab is a chimeric monoclonal antibody composed of a murine variable region attached to human Fc (constant) portion of IgGκ. Adalimumab is a fully humanized monoclonal antibody, dosed every second week as a subcutaneous injection. While etanercept is a fusion protein produced by recombinant DNA. It fuses the TNF receptor to the constant end of the IgG1 antibody. On the other hand, Certolizumab pegol is a humanized antigen binding fragment (Fab′) of a monoclonal antibody that has been conjugated to polyethylene glycol [6]. Finally, Golimumab is a human immunoglobulin G1 kappa (IgG1) monoclonal antibody specific for human tumor necrosisfactor (TNF; TNF α) [7]. Concerns were present toward increased risk for infections, malignancy and cardiovascular disease with the use of anti TNF-α. However, one study demonstrates that among 16,000 patients treated with anti TNF-α for rheumatoid arthritis there was no increase of the serious bacterial infections in comparison to patients treated with methotrexate (MTX) [8]. Overall, the use of anti TNF α is associated with an increased risk of infections. Caution should be addressed while using these drugs in daily clinical practice. Regarding the risk of malignancy; recent analysis from Lombardy Rheumatology Network (LORHEN) registry addressed no increase in the malignancy risk in comparison to the general population, however the risk of hematological malignancy especially lymphoma was significantly increased in people who are older than 65 years [9].

In comparison to conventional DMARDs; anti TNF-α agents do not increase the risk for cardiovascular events [10]. Table 1 summarizes the all available anti TNF-α agents used in treatment of vasculitis.

In this article, we have conducted extensive review of different publications that addressed the use of anti TNF-α agents in vasculitis as shown in (Figure 1). Aiming to deliver a comprehensive overview of the best and the latest evidence in this field.

Takayasu Arteritis

Takayasu arteritis (TA) is an idiopathic panarteritis affects the large and medium vessels especially the aorta and its branches, with onset of age before 30. It is characterized by granulomatous inflammation in the involved site [11]. TNF-α is an important cytokine for granuloma formation. Activated T cells, natural killer cells, γδ cells and macrophages are also important pathophysiological principles of TAs.
development [11]. The mainstay therapy consists of glucocorticoid (GC) and methotrexate (MTX) [12]. Only 40–60% of patients with TA achieve remission on conventional therapy [12]. Thus, the need for a new modality of treatment is warranted to achieve remission in the remaining patients. The clinical benefit of anti TNF-α in TA has been demonstrated via several case reports and series. One case series observed 15 patients with resistant TA [13], in all patients who received GC the relapses were observed while the dose was tapered down. In this study, patients were divided into two groups, 7 patients received etanercept, the remaining 8 patients were started on infliximab. Out of these 15 patients, 93% showed significant improvement, while 67% experienced GC-free remission for 3 years after follow-up. Another case series described the effect of anti TNF-α on TA [14]. Five patients with TA failed to achieve remission on conventional therapy. Infliximab was initiated with MTX as a concomitant immunosuppressive agent in 4 cases, one case was on AZA. The follow-up duration was ranging from 3 to 72 months. It showed only one relapsed case. The other four cases showed successful tapering of GC dose with no relapse upon follow-up. Additionally, a literature review of 79 cases with TA showed significant response on infliximab and etanercept [14]. Global improvement was observed in 90%, complete remission in 37% and partial remission in 53%, patients who do not respond to anti TNF-α therapy were only 9%. One study evaluated 8 patients with refractory TA; two of them were refractory to infliximab therapy and 3 patients did not achieve remission on GC and MTX. However, all patients received tocilizumab (interleukin-6 receptor antagonist) therapy and the follow-up showed 7 out of 8 patients achieved remission. This data shows an interesting finding that tocilizumab can be a potential therapy for refractory TA to anti-TNF-α therapy [15]. Case series of 10 patients showed a sustainable remission on tocilizumab therapy in 60%, the other 40% failed to satisfy the criteria of sustainable remission, requiring either clinical or biochemical criteria of remission [16]. Interestingly, out of 6 patients who achieve sustainable remission on tocilizumab underwent follow-up after discontinuation, only 2 patients maintain their complete remission on post-tocilizumab follow-up period (3-14) months [16]. These finding can raise the concerns regarding the effectiveness of tocilizumab as a steroid-sparing agent.

In conclusion, anti TNF-α can be a potential therapy for patients with steroid-resistant TA. However, relapsed cases on anti TNF-α agents were reported as well. Tocilizumab can be a potential option in these cases, although there are reports of relapses after holding the tocilizumab. Overall, further placebo-controlled studies should be conducted to improve the current quality of evidence available for practicing clinicians. Table 1 shows a summary of studies that addressed the use of anti TNF- in patients with TA [17-21].

### Table 1: Summary Of Anti-TNF α Agents In Systemic Vasculitis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Side effects</th>
<th>Pregnancy considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Binding antibody (chimeric IgG1). Thereby interfering with endogenous TNF-α.</td>
<td>Headache (18%), Increased serum ALT, Increased ANA titer and infections.</td>
<td>Category B</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Recombinant DNA-derived protein composed of tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1.</td>
<td>Headache (17%), Skin rash, abdominal pain and infections</td>
<td>Category B</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Recombinant DNA-derived human immunoglobulin G1 (IgG1) monoclonal antibody specific for human tumor</td>
<td>Hepatitis B infection reactivation, Exacerbation of demyelinating diseases,</td>
<td>Category C</td>
</tr>
</tbody>
</table>

Out of these 15 patients, 93% showed significant improvement, while 67% experienced GC-free remission for 3 years after follow-up. Another case series described the effect of anti TNF-α on TA [14]. Additionally, a literature review of 79 cases with TA showed a significant response to infliximab and etanercept [14]. Global improvement was observed in 90%, complete remission in 37% and partial remission in 53%, patients who do not respond to anti TNF-α therapy were only 9%. One study evaluated eight patients with refractory TA; two of them were refractory to infliximab therapy, and three patients did not achieve remission on GC and MTX. However, all patients received tocilizumab (interleukin-6 receptor antagonist) therapy, and the follow-up showed 7 out of 8 patients achieved remission. This data shows an interesting finding that Tocilizumab can be a potential therapy for refractory TA to anti-TNF-α therapy [15]. Case series of 10 patients showed a sustainable remission on tocilizumab therapy in 60%, the other 40% failed to satisfy the criteria of sustainable remission, requiring either clinical or biochemical criterion of remission [16].
follow-up duration was ranging from 3 to 72 months. It showed only 7 out of 8 patients who achieved complete remission in 37% and partial remission in 53%, patients who do not respond to anti TNF-α therapy were only 9%. One study showed significant response on infliximab and etanercept [14]. Global improvement was observed in 90%, complete remission in 37% and partial remission in 53%, patients who do not respond to anti TNF-α therapy were only 9%. One study evaluated 8 patients with refractory TA; two of them were refractory to infliximab and etanercept [14].

Golimumab
- monoclonal antibody that binds to human tumor necrosis factor alpha (TNFα)
- Positive ANA titer, Leukopenia, High serum ALT.
- Category B

Table 1: Summary of different agents under Anti TNF-α class.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Date</th>
<th>Methodology</th>
<th>Used agent</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinickia et al.</td>
<td>Retrospective analysis from medical records</td>
<td>2016</td>
<td>Ten patients were identified, who fulfill the ACR diagnostic criteria for GCA, TA</td>
<td>Infliximab, Etanercept and Tocilizumab</td>
<td>Sustained remission was achieved in all cases during follow-up (mean follow-up 59.6 ± 27.2 months) with decrease in Glucocorticoid dose in 70%. One patient discontinued Infliximab due to recurrent infections - One patient with neutropenia</td>
</tr>
<tr>
<td>Abisror et al.</td>
<td>Retrospective analysis and review of the literature</td>
<td>2013</td>
<td>Five patients multicentric cases, another 39 cases from review of the literature</td>
<td>Tocilizumab</td>
<td>Remission in 93% of the cases, 78% at 6 months and 75% at the time of last visit (11 months), Mild Neutropenia</td>
</tr>
<tr>
<td>Alberto Can’as et al.</td>
<td>Retrospective analysis of 8 patients</td>
<td>2014</td>
<td>Eight patients who treated with tocilizumab for median duration of 18 months were reviewed from the records between 2010 and 2013</td>
<td>Tocilizumab</td>
<td>. All the eight patients showed global improvement. Three patients have needed adding immunosuppressive after TCZ therapy</td>
</tr>
<tr>
<td>Nakaoka et al.</td>
<td>Prospective study for four patients</td>
<td>2013</td>
<td>From June 2008 till February 2011. Four patients were identified as Glucocorticoid resistant Takayasu arteritis started on TCZ therapy</td>
<td>Tocilizumab</td>
<td>Significant reduction in the thickening of vessel walls in 2 patients. All the patients attained outstanding reductions in the prednisolone doses</td>
</tr>
</tbody>
</table>

Giant Cell Arteritis

Giant cell arteritis (GCA) is a most common form [22,23] as a multisystem granulomatous vasculitis predominantly targets large and medium sized arteries [24,25]. Classical disease therapy relies on a high dose of GC administration once the clinical finding is suggestive of the disease [25,26]. Relapse is common in 60-70% of patients thus, other therapeutic modalities are required [23,27,28]. A meta-analysis in 2014 [29], included five studies about anti TNF alpha agents in GCA. It failed to prove any beneficial effect. Table 3 shows a summary of studies that addressed the use of anti TNF-α agents in patients with GCA [30-32].

Behçet’s Disease

Behçet’s Disease (BD) is an inflammatory disorder characterized by recurrent oral aphthous ulcer and systemic manifestations: genital ulcer, skin lesion and neurological manifestations [33]. The ability of BD to involve more than one type of vessels makes it unique and remarkable vasculitic disease.
Comarmond [14]  
Retrospective analysis and review of the literature  
2012  
84 patients (5 personal cases and 79 patients from the literature) with refractory Takayasu arteritis treated with anti TNF-α  
Infliximab, Etanercept  
Thirty one patients achieved complete remission, 45 patients labeled as partial responders and eight were non-responder. -8 patients with infections, 4 with hypersensitivity,1 immune reaction, 1 breast cancer, 1 Nausea and diarrhea, 1 cardiac failure

Goel et al. [16]  
Retrospective analysis  
2013  
Medical records for 10 patients Takayasu arteritis who received Tocilizumab therapy were reviewed and analyzed.  
TCZ  
7 patients reached sustainable remission, 3 relapsed patients. Remission was not maintained after discontinuation of TCZ. -One patient with transient skin rash, transient transaminitis, .

Nunes et al. [21]  
Retrospective analysis  
2010  
IFX  
Out of 15 patients only 3 received TNF blocker agents due to steroid-Resistant disease. Shows a complete remission upon follow up - No documented adverse effects

Table 2: Summary of the studies that investigate using of anti TNF-α agents in Takayasu arteritis.

The current therapeutic modalities for BD came from case reports and case series, with few follow-up studies. Currently, for minor disease manifestations; a regimen consists of colchicine initially and GC for patients who do not respond well for colchicine [34,35]. For major disease manifestations; typical regimen is high dose of GC (1 mg/Kg/day) not exceeding 80 mg/day. The effect of anti TNF-α in BD has been investigated thoroughly, the beneficial effect of infliximab, adalimumab, and etanercept was reported [36,37]. In a multicenter observational study including 164 patients with BD with uveitis received infliximab for more than a year, infliximab was found reducing the number of ocular attacks per year [38].
Table 3: Summary of the studies that investigate using of anti TNF-α agents in Giant cell arteritis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Date</th>
<th>Methodology</th>
<th>Used agent</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takeuchi et al. [38]</td>
<td>Prospective analysis</td>
<td>2014</td>
<td>A total of 164 consecutive patients with BD treated with infliximab for more than 1 year were studied. The mean treatment duration was 32.9±14.4 months.</td>
<td>Infliximab</td>
<td>60% relapse in uveitis cases after first year, Control was made in 90% of the cases later on by increasing topical steroid and infliximab doses.</td>
</tr>
<tr>
<td>Lee et al. [39]</td>
<td>Retrospective non-controlled review of medical records</td>
<td>2013</td>
<td>28 patients with intestinal BD who received at least 1 dose of Infliximab. Response rates of Infliximab at 2, 4, 30, and 54 weeks for each patient were investigated</td>
<td>Infliximab</td>
<td>The clinical response rates at 2, 4, 30, and 54 weeks were 75%, 64.3%, 50%, and 39.1%, respectively.</td>
</tr>
<tr>
<td>Cantini et al. [43]</td>
<td>Prospective analysis</td>
<td>2012</td>
<td>Single center, prospective, 6-year duration, follow-up study on 50 consecutive patients</td>
<td>Infliximab</td>
<td>A complete response was recorded in 34/50 (68%) patients and partial response in 11/50 (22%). Five patients were nonresponders No serious side effects</td>
</tr>
<tr>
<td>Melikoglu et al. [40]</td>
<td>Double blind, placebo controlled study.</td>
<td>2005</td>
<td>Forty male patients with BD, were randomized (20 patients to each study arm) to receive either Etanercept 25 mg twice a week or placebo for 4 weeks</td>
<td>Etanercept</td>
<td>More patients remained free of oral ulcers (45% versus 5%). -More patients remained free of nodular skin lesions (85% versus 25%).</td>
</tr>
<tr>
<td>Bawazeer et al. [41]</td>
<td>Retrospective review of records.</td>
<td>2010</td>
<td>Twenty-one eyes of 11 male patients with ocular Behçet disease received Adalimumab therapy.</td>
<td>Adalimumab</td>
<td>Ten out of 11 patients showed complete resolution of inflammation by 4 weeks. The dosage of steroid and immunosuppressive drugs were reduced, then stopped in 3 and 6 patients respectively.</td>
</tr>
<tr>
<td>Olivieri et al. [34]</td>
<td>Prospective, longitudinal and observational study</td>
<td>2011</td>
<td>Data were collected on every patient with BD beginning anti-TNF therapy in the last 8 years. Patients should be switched to Adalimumab after failing or not tolerating Infliximab.</td>
<td>Adalimumab</td>
<td>Initially 69 treated with Infliximab, lack of response or infusion reaction necessities administration of Adalimumab, out of those 17, nine patients showed sustained remission and 3 patients with good response.</td>
</tr>
</tbody>
</table>

Table 4: Summary of the studies that investigate using of anti TNF-α agents in Behçet's disease.

Cryoglobulinemic Vasculitis

It is a systemic inflammatory condition that involve small to medium sized vessel vasculitis caused by cryoglobulin contained immune complex deposition [44]. Conventional treatment of this vasculitis started by treatment of underlying cause as in hepatitis C virus (HCV)-associated cryoglobulinemic vasculitis [45]. Rituximab (RTX) (Anti-CD20) showed benefit in life threatening conditions [46].

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while CYC reserved for refractory cases to antiviral or RTX. Anti-TNF agents have a promising effect. Infliximab showed positive effect in one reported case that failed to achieve remission on conventional therapy [47].

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>Publishing Date</th>
<th>Materials and Methods</th>
<th>Used Agents and Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartolucci et al. [48]</td>
<td>Prospective study</td>
<td>2002</td>
<td>Ten patients with different vasculitis, one case had cryoglobulinemic vasculitis, with active disease or new flare despite conventional therapy.</td>
<td>Infliximab 5 mg/kg at day1, 14, 42, and Q8 weekly. Evaluated by BVAS score.</td>
<td>Symptomatic improvement. No side effect.</td>
</tr>
<tr>
<td>Koukoulaki et al. [49]</td>
<td>Case report</td>
<td>2005</td>
<td>Young women known case of cryoglobulinemic vasculitis on conventional therapy developed intestinal vasculitis and significant GI bleeding</td>
<td>Single dose of Infliximab 5 mg/kg</td>
<td>Stabilization of patient bleeding and HB level and discharge home.</td>
</tr>
</tbody>
</table>

Table 5: Summary of the studies that investigate using of anti TNF-α in cryoglobulinemic vasculitis.

Single dose of infliximab 5mg/kg results in complete resolution of the symptoms; followed by uneventful clinical course for one patient complaining of cryoglobulinemic vasculitis with gastrointestinal bleeding. Table 5 shows a summary of studies that addressed the use of anti-TNF-α agents in patients with cryoglobulinemic vasculitis [48,49].

Kawasaki Disease

Kawasaki disease (KD) is a form of medium sized vasculitis most commonly affects coronary arteries. In children KD is the second most common vasculitis [50]. Marked elevation of serum TNF-α found in sera of KD patients [51].

Acute KD management strategy involves administration of 2 g/kg as a single infused intravenous immunoglobulin (IVIG) with high dose aspirin. Aspirin can be continued as a low dose until echocardiograms is normal [52]. Almost 15-20% of patients failed to respond to initial IVIG [52]. In those refractory KD patients, anti TNF-α agents have been investigated [53]. Several retrospective studies, case series, and case reports addressed infliximab effectiveness in refractory KD.

From 2004-2006 [54], 24 patients with refractory KD received either infliximab or a second dose of IVIG. Each group contained 12 patients. Symptoms subsided in 11 patients on infliximab group versus in 8 who were on IVIG. Two out of 4 who did not respond were in IVIG group, had responded to infliximab later on. Another 2 studies addressed the effect of adding infliximab to the standard therapy. In 2014 [55] a phase 3, randomised, double-blind, placebo-controlled trial was conducted on 196 patients to assess the benefit adding of infliximab to the conventional therapy. The results came to show infliximab didn’t reduce the disease resistance rate. Etanercept is an under-studied anti TNF-α agent for refractory KD. A prospective open label trial of 17 patients with KD [56], all enrolled patients received IVIG plus aspirin, etanercept was administrated immediately after IVIG infusion. No complications or side effects have occurred in all 15 patients. Table 6 shows a summary of studies that addressed the use of anti TNF-α agents in patients with Kawasaki disease [57-63].

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Date</th>
<th>Materials and Methods</th>
<th>Used Agent and dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns et al. [74]</td>
<td>Retrospective study</td>
<td>2005</td>
<td>16 US patients resisted initial IVIG</td>
<td>Infliximab 5 mg/kg</td>
<td>81.25% of patients (13) responded well to single infusion of Infliximab. No reported side effects. CRP declined in 10 patients after 48 hours on infliximab infusion</td>
</tr>
<tr>
<td>Burns et al. [58]</td>
<td>A multi centers Randomized Controlled Trial.</td>
<td>2005</td>
<td>24 refractory KD cases failed 1st IVIG. Either Infliximab or a 2nd dose of IVIG was given. Each group contained 12 patients.</td>
<td>Infliximab 5 mg/kg</td>
<td>Symptoms subsided in 11 Patients on Infliximab and 8 on IVIG. Two out of 4 who did not respond to IVIG had responded to infliximab. Side effects related to disease course developed in 18 patients. Transient hepatomegaly with spontaneous resolution reported in 10 patients (couldn’t be ruled out before treatment) No significant differences between the 2 drugs.</td>
</tr>
<tr>
<td>Song et al. [59]</td>
<td>Retrospective study</td>
<td>2004-2008</td>
<td>16 KD patients in Korea</td>
<td>5-6.6 mg/kg of Infliximab</td>
<td>13 cases resolve completely. 2 cases achieved permanent resolution of arthritis</td>
</tr>
</tbody>
</table>
At least 2 doses of IVIG were given with or without steroid
14 patients had decreased CRP after Infliximab
Coronary artery lesions found in 15 of 16 before Infliximab, dilatation was stopped or delayed after Infliximab.
No infusion reactions or complications were noted in all patients
1 case only developed acute hepatitis during treatment and calculus cholecystitis 4 months later

Son et al. [60] retrospective study 2011 106 refractory KD failed to respond to 1st IVIG dose. 20 patients received Infliximab compared to 86 patients received 2nd IVIG. Infliximab 5 mg/ kg Infliximab patients had fewer days of fever and shorter hospital stay.
Both groups were similar in coronary artery size after 6 weeks, also in adverse effects

Mori et al. [57] open label case series 2012 20 patients received Infliximab after failure of IVIG therapy Infliximab, 5 mg/kg Rapid symptomatic improvement in 18 patients, subsided inflammatory mediators. And Mildly dilated coronary artery returns to normal after 1 month of Infliximab. No reported side effects or complications

Burns et al. [61] randomized clinical trial 2013 7 KD patients received IVIG and 7 KD received IVIG in addition to infliximab Infliximab (5 mg/kg) no adverse effect on immunological cells associated with Infliximab treatment

Tremoulet et al. [62] Phase 3 randomized, double-blind, placebo-controlled trial 2014 98 patients received Infliximab in addition to placebo plus standard therapy. Infliximab 5 mg Ag Infliximab group had better outcomes, no infusion reaction to IVIG compared with 13.4% in Placebo group. Resistance to IVIG treatment in KD did not reduce after Infliximab addition

Youn et al. [63] Randomized controlled trial 2016 43 KD patients resisted 1st dose of IVIG. 32 KD received second dose of IVIG compared to 11 KD who received infliximab Infliximab 5 mg Ag Better response was noticed in Infliximab group in term of shortening the duration of fever and hospitalization, 90.9% and 65.6% respectively
Similar adverse events and coronary artery outcomes

Table 6: Summary of the studies that investigate using of anti TNF-α agents in Kawasaki disease.

Polymarteritis Nodosa

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that typically affects small and medium-sized arteries [64]. The treatment and the prognosis are highly variable depending on the extent of the disease if it is systemic or localized to the skin. Despite aggressive medical management with GC and CYC, many patients develop aggressive disease refractory to all available modalities with high incidence of mortality reaching up 22.4% within five years from the disease onset [65]. Several reported cases showed remission after failing of conventional therapy [65-67]. The selected cases cover a broad spectrum of clinical presentation representing different age groups. In each case, patients were treated with one or a combination of GC and immunosuppressant with little or no response to treatment.
Use of anti TNF-α agents in Polyarteritis nodosa.

Few cases were treated with etanercept [65-67], one with infliximab [68], tocolizumab [69], adalimumab [70] and lastly, a case treated with rituximab [71]. All cases showed a good response to treatment with achieved remission upon clinical and biochemical basis without serious side effects. Although we found no prospective studies or large trials addresses the role of anti-TNF in inducing or maintaining remission in patients with PAN, there are several case reports that suggest the benefits of anti-TNF-alpha in severe and refractory cases. More studies are required to determine the safety and efficacy of anti-TNF treatment in PAN. Table 7 shows a summary of studies that addressed the use of anti TNF-α agents in patients with PAN.

**Table 7:** Summary of the studies that investigate using of anti TNF-α agents in Polyarteritis nodosa.

<table>
<thead>
<tr>
<th>Case report</th>
<th>Year</th>
<th>Patient Description</th>
<th>Treatment</th>
<th>Remission/Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeffrey et al.</td>
<td>2005</td>
<td>Young male with refractory systemic PAN for 9 years despite treatment with corticosteroid, and CYC.</td>
<td>Etanercept 50 mg/SC weekly</td>
<td>Remission</td>
</tr>
<tr>
<td>Al-Bishri et al.</td>
<td>2005</td>
<td>Young Female diagnosed as a severe (PAN) with visceral involvement. She received high doses of corticosteroid and CYC with no response.</td>
<td>Infliximab 3mg/kg at 0,2, and 6 weeks then every 8 weeks</td>
<td>Remission</td>
</tr>
<tr>
<td>Takeshi et al.</td>
<td>2012</td>
<td>Sixty years old female with PAN with hep B Received intensive treatment of Prednisolone, CYC, AZA; Tacrolimus IVIG &amp; plasma exchange</td>
<td>Etanercept 25 mg/kg sc weekly lamivudine 100 mg/day</td>
<td>Remission With no reactivation of hepatitis B</td>
</tr>
<tr>
<td>Watanabe et al.</td>
<td>2016</td>
<td>3-year-old male, PAN with vertebal artery vasculitis, treated with methylprednisolone and CYC.</td>
<td>Tocilizumab 4 mg/kg q 4week</td>
<td>Remission was achieved within 7 month.</td>
</tr>
<tr>
<td>Seri et al.</td>
<td>2015</td>
<td>59 male patients with PAN treatment failed on steroid and CYC</td>
<td>RTX 375 mg/m2 IV infusion Weekly</td>
<td>Remissions</td>
</tr>
<tr>
<td>Almoallim et al.</td>
<td>2009</td>
<td>18 years old male with PAN and gangrenous fingers, was in refractory to different treatment with prednisolone, MTX, MMF and CYC.</td>
<td>Adalimumab 40 mg subcutaneously every two weeks. Maintenance on MMF</td>
<td>Remission after the fourth injection.</td>
</tr>
</tbody>
</table>

**Conclusion**

Use of anti TNF-α agents is a promising modality in the field of vasculitis management. Despite lacking of well-conducted randomized controlled trials in several vasculitic disorders, anti TNF-α agents remain an optional therapy for difficult-to-treat cases. It has to be noted that anti-TNF alpha agents showed no beneficial effects in ANCA-associated vasculitits (AAV) [72]. In fact, these agents can induce autoimmune syndromes like vasculitis e.g. Henoch-schönlein purpura [73]. Collectively, we encourage clinicians, in the field of taking care of vasculitis patients, to raise their collaboration level; with the aim to reach a better evidence-based clinical practice.

**References**


