SMGroup

Use of Anti TNF-α Therapy in Systemic Vasculitis

Talal Al-Mteri[1], Fatma Al-shaiki[2], Shahad Hafiz[1], Rabab Taha[3] and Hani Almoallim[1,3,4]*

[1]Department of Medicine, Umm Al-Qura University, Saudi Arabia

[2]Department of Internal Medicine, King Fahad general hospital, Saudi Arabia

[3]Department of Medicine, Dr. Soliman Fakeeh Hospital, Saudi Arabia

[4] Alzaidi Chair of Research in Rheumatic Diseases, Umm-Al Qura University, Saudi Arabia

*Corresponding author: Hani Almoallim, Alzaidi Chair of Research in Rheumatic Diseases, Faculty of Medicine, Umm-Al Qura University, Makkah, Saudi Arabia, Email: hanialmoallim@gmail.com

Published Date: October 18, 2016

INTRODUCTION

There are several vascultic 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 demanded since it might be a life threatening conditions and the patient could die from the disease itself or as a long term consequence from pharmacological interventions. However, the available studies to provide evidence of therapies to practicing clinicians are mostly based on non-randomized controlled trials. Due to the rarity of the vasculitis, having a statistical power by large number of patients is a major issue to conduct well-controlled randomized clinical trial [2]. One of challenges to conduct a well-controlled randomized clinical trial is the difficulty to establish an inclusion criterion for patients with primary vasculitis since a solid measurable data like (histopathological studies, laboratory markers) do not exist for every single patient in the daily clinical practice, for example large vessel vasculitis lack for specific serological markers [3].

Failure to establish a measurable endpoint in vasculitic disorders remains an issue to conduct randomized controlled trials. Variation in determination of the endpoint in different trials makes obtaining and comparing between them is difficult. Some trials try to answer the same clinical question by using two different endpoints to examine the validity of that trial [4,5]. For example in induction trials the remission rates are used as an endpoint, while in maintenance trial the time to relapse are often used, the issue is the lack of standardized definition of remission or relapse. Several immunological and histological studies have shown the circulating and tissue bounds immune complexes [6].

Tumor necrosis factor is a pro-inflammatory cytokine primarily by ipopolysaccharide-stimulated macrophages and monocytes [7]. TNF-α is a key inflammatory cytokine 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 [8].

The available anti-TNF-α including 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 and is dosed every second week as a subcutaneous injection. Etanercept is a fusion protein produced by recombinant DNA It fuses the TNF receptor to the constant end of the IgG1 antibody. Certolizumab pegol is a humanized antigen-binding fragment **(Fab')** of a monoclonal antibody that has been conjugated to polyethylene glycol [9]. Golimumab is a human immunoglobulin G1 kappa **(IgG1)** monoclonal antibody specific for human tumor necrosis factor (TNF; TNF-α) [10]. Since TNF-α plays a major role in development of granulomatous inflammation Etanrcept can be a promising modality to eradicate systemic vasculitis especially those with granulomatous inflammation including giant cell arteritis **(GCA)**, Takayasu Arteritis **(TA)** and granulomatosis with polyangitis **(GPA)** [11].

Concerns were present toward increase 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)** [12]. 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 [13]. In comparison to conventional DMARDs; anti TNF-α do not increase the risk for cardiovascular events [14].

In this chapter we aim to review the various uses of anti TNF-α in vasculitic disorders in order to deliver a comprehensive review for the best and high quality of evidence for using of anti TNF-α in vasculitis. We have conducted extensive review of various publications addressing the uses of anti TNF-α in vasculitis. We summarized the findings based on different vasculitic disorders using mainly (The 2012 Chapel Hill consensus conference on nomenclature of vasculitis) Classification system [3]. We are going to describe how these agents were used and what sort of outcomes was expected and potential issues and/or side effects while using them. (Table 1).

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

Agent	Mechanism of action	Side effects	Pregnancy considration
Infliximab	Binding antibody(chimeric IgG1).thereby interfering with endogenous TNF-α	Headache (18%), Increased serum ALT, Increased ANA titer and infections.	Category B
Etanercept	Recombinant DNA-derived protein composed of tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1.	-Headache (17%), Skin rash,Abdominal pain and Infections	Category B
Adalimumab	recombinant DNA-derived human immunoglobulin G_1 (IgG_1) monoclonal antibody specific for human tumor necrosis factor (TNF-α)	Hepatitis B infection reactivation, Exacerbation of demyelinating diseases, Pancytopenia, Infection	Category C
Certolizumab	Certolizumabpegol binds to and selectively neutralizes human TNF-alpha activity.	Aplastic anemia, thrombocytopenia, Antibodies to Certolizumab.	Category B
Golimumab	monoclonal antibody that binds to human tumor necrosis factor alpha (TNFα)	Positive ANA titer, Leukopenia, High serum ALT,	Category B

TAKAYASU ARTERITIS

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 [15]. TNF-α is important for formation of granuloma. Activated T cells, natural killer cells, γ/δ cells and macrophages are important pathophysiological principles of TA's development [15]. The mainstay therapy consists of glucocorticoid **(GC)** and MTX [16]. Unfortunately only 40-60% of patients with TA achieve remission with a good percentage of patients remain refractory to conventional therapy [15]. Thus, the need of new modality of treatment is emerging to achieve remission in the remaining 40%. Patients with steroid-resistant TA underwent a trial of azathioprine **(AZA)**, MTX and mycophenolate mofetil **(MMF)**, resulting in observed improvement in 20% of patients only [15]. The clinical benefit of anti TNF-α in TA has been demonstrated via several case reports and case series. One case series observed 15 patients with resistant TA [17], in all patients who received GC the relapses were observed while tapering the dose down. In this study, patients were divided into two groups, 7 patients received etanercept, another 8 patients were started on infliximab. Of these 15 patients, 93% showed significant improvement, while 67% experienced GC-free remission for 3 years after follow-up. Two infections were reported among these 15 patients, with one injection site reaction. There was also several case reports reveal

marked improvement for patients with TA while they underwent TNF inhibition for other reasons rather than TA [18]. Another case series has been published to describe the effect of anti TNF-α on TA [19]. The five patients who met the American College of Rheumatology **(ACR)** criteria for TA failed to achieve remission on conventional therapy [20]. Infliximab was initiated to examine the efficacy of anti-TNF-α in resistant TA, MTX was used as a concomitant immunosuppressive agent in 4 cases, and one case was on AZA. The follow-up duration was ranging from 3 to 72 months and showed only relapses in one case, the other four cases underwent a significant improvement on clinical and laboratory parameters with no relapses and successful tapering of GC dose. In addition, a literature review of 79 cases with TA treated with anti TNF-α showed a significant response in patients who received infliximab and etanercept therapy [19]. Global improvement was observed in 90%, with complete remission in 37% and partial remission in 53%, patients who do not respond to anti TNF-α therapy were only 9%. The non-responder patients revealed an interesting finding that TA can be even resistant to TNF inhibition. This literature review faces a limitation to examine the effectiveness of anti TNF-α since different case series and reports use different endpoint follow-up resulting in various outcomes. Another analysis of ten cases received anti-TNF-α after unfavorable response on GC therapy [21]. Five patients with TA and another five with GCA, five patients started on infliximab, another four on tocillizimab and one on etanercept. Remission was observed in all ten patients in terms of clinical and biochemical parameters with successful tapering of prednisolone **(PRD)** therapy, four out of ten cases discontinued PRD therapy at the time of last follow-up. A systematic review of 25 studies evaluated the role of biological therapy in large vessel vasculitis including TA and GCA. In 11 case series of 75 patients with TA, 74.7% achieved remission on infliximab and 32% discontinued their GC therapy. Another four case series of 11 patients underwent a tocilizumab course, 91% achieved remission including one patient with tocilizumab monotherapy, and two relapses were noted during the follow-up period. On the other hand 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, a total of 8 patients received tocilizumab therapy underwent a follow up with total duration of 18 months. Radiological, biochemical and clinical markers showed 7 out of 8 patients achieved remission on tocilizumab therapy. This data shows an interesting finding that tocilizumab can be a potential therapy for refractory TA to anti-TNF-α therapy [22]. 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 [23]. Interestingly, out of 6 patients who achieve sustainable remission on tocilizumab underwent follow-up after discontinuation of tocilizumab, only 2 patients maintain their complete remission on post-tocilizumab follow-up period (3-14) months [23]. 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 target therapy for patients with TA especially for patients with steroid-resistant disease. There are reported cases of relapse on anti TNF-α agents.

Tocilizumab can be a potential option in these cases. Overall, further placebo-controlled studies should be conducted to improve the current quality of evidence available for practicing clinicians. There are obvious limitations given the rarity of this vasculitic disorder. (Table 2).

Table 2: Summary of the studies that investigate using of TNF blocker in Takaysu arteritis.

Author	Study type	Date	Methodology	Used agent	Outcomes
Juan P, Vinickia et al. [21]	Retrospective analysis from medical records	2016	Ten patients were identified, who fulfill the ACR diagnostic criteria for GCA, TA	Infliximab, Etanerecpet and Tocilizumab	Sustained remission was achieved in all cases during follow-up (mean follow-up 59.6 ± 27.2 months) with decrease in Glucocorticoid dose. in 79% of the patients. _ One patient discontinued infliximab due to recurrent infections - One patient with neutropenia and onother developed anaphylaxis
Abisror N, et al. [24]	Retrospective analysis and review of the literature	2013	Five patients multicentericcases, another 39 cases from review of the literature	Tocilizumab	Clinical and biological activities significantly decreasedwithin 3 months in 93% of the cases, 78% at 6 months and 75% at the time of last visit (11 months). Mild Nutropenia
Carlos Alberto Can˜ as, et al. [22]	Retrospective analysis of 8 patients	2014	Eight patients who trerated with tocilizumab for median duration of 18 months were reviewed from the records between 2010 and 2013	Tocilizumab	Tocilizumab were continued until the last visit. All the eight patients showed global improvement. Three patients have needed adding immunosuppressive after TCZ therapy
Nakaoka Y, et al. [25]	Prospective study for four patients	2013	From June 2008 till February 2011, Four patients were identified as Glucocorticoid resistant Takayasu arteritis started on TCZ therapy	Tocilizumab	the cross-sectional imaging by MRI and CT scanning revealed significant reduction in the thickening of vessel walls in 2 patients. All the patients attained outstanding reductions in the prednisolone doses without any signs of clinical relapse of TA during the TCZ therapy
Comarmond C [19]	Retrospective analysis and review of the literature	2012		Infliximab, Etanercept	- 31 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 R.,et al. [23]	Retrospective analysis	2013	Medical records for patients Takayasu arteritis who received Tocilizumab therapy were reviewed and analyazed.	TCZ	7 patients reached sustainable remission, 3 relapsed patient. Remission was not maintained after discontinuation of TCZ. - None of the patients had serious adverse events. One patient with transient skin rash, transient transaminitis, uncomplicated urinary tract infection and upper respiratory tract infection.
Nunes G, et al. [26]	Retrospective analysis	2010	Review medical files of 15 patients who attend Rheumatology clinic for Takayasu arteritis between July,2007- July, 2008	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

GIANT CELL ARTERITIS

Giant Cell Arteritis **(GCA)** is a systemic granulomatous vasculitis that affects large and medium sized arteries, most commonly affecting aorta and its branches [27,28] . It is the most common form of vasculitis [29,30]. Acute visual loss is one of the serious but preventable complications occurs in one fifth of the patients [30,31]. The exact pathogenesis of the disease is not well understood [28,32]. Vascular inflammation has been found to be triggered by inflammatory mediators. Hence, the thromboembolic disease activity has been linked to them [32,33]. IL-1, TNF alpha and IL-6 are proven to cause temporal arteritis in GCA patients [27,32]. High magnitude of these inflammatory mediators correlates with intense inflammation [27,28]. The higher TNF alpha tissue and serum concentration the longer GC treatment duration is required [27,28].

Standard disease management depends on induction of high dose GC once the diagnosis is suspected; rapid relief of symptoms can be a diagnostic clue to GCA [28,34]. GCA is one of the most common long term steroid dependent disease together with polymyalgia rheumatic **(PMR)** [31]. Once the acute inflammation subsided a slow tapering of PRD occurs and the steroid continued for 2 to 3 years [29,33]. But unfortunately 60-70% of patients failed to achieve complete remission [28,32], with majority of cases develop corticosteroid-related morbidity including hypertension, diabetes and metabolic syndrome [34]. Recurrent relapse or failure to wean GC dose requires adjunctive therapy as methotrexate MTX or other immunosuppressant according to the guidelines [30,31], raising the need for another effective and safe treatment modality.

Evidence of TNF alpha involvement in disease pathology opened a new window on suggestive treatment of GCA using anti-TNF-α agents, several agents have been reported to be used: infliximab, etanercept and adalimumab [28]. Promising effective results have been reported initially in different single cases [32,33]. In 2014, a meta-analysis investigated 95 GCA patients who received biological agents. Five studies out of 25 enrolled in this meta-analysis were about anti TNF alpha

agents in GCA. In this analysis no beneficial effect was demonstrated upon using of anti-TNF agents (infliximab, etanercept and adalimumab) in patients with GCA [35]. In conclusion, the consistent evidence that support the routine use of anti-TNF-α agents in GCA is lacking, however, the available evidence fails to show superiority of anti-TNF-α agents over conventional therapy. (Table 3 summarizes the current available literatures that investigate using of anti TNF-α in GCA).

Table 3: Summary of the studies that investigate using of TNF blocker in GCA.

Author	Type of Study	Date	Methodology	Used Agents	Outcomes
Hoffman, GS et al.	RCT	2007	44 GCA patients were on glucocorticosteroid-induced remission 28 patients received corticosteroid plus infliximab and 16 patients received corticosteroid plus placebo	Infliximab 5mg/kg	• Infliximab group relapse rate at week 22 did not decrease compared to placebo group. 43%, 50% respectively • Steroid dosage tapering to 10mg/ d without relapse was 61% in Infliximab group compared with 75% in placebo group. • Infection incidence was 71% in Infliximab group and 56% with placebo.
Martinez tapoada et al.	RCT	2008	17 GCA patients, 8 received etanercept and 9 received placebo over 12 months together with corticosteroids.	Etanercept 25 mg subcutaneously, 2times/week	• After 1 year, diseased was controlled without steroid in 50% of patients on Etanercept and in 22,2% of placebo patients. • Steroid dose was significantly lower in Etanercept group. • Side effects were similar between the 2 group
Seror R, et al.	RCT	2013	70 patients, 34 received adalimumab and 36 received placebo. All in addition to prednisolone	Adalimumab 40 mg SC for 10 weeks	• 20 patients in adalimumab group and 18 in the placebo achieved remission at week 26 • Relapse free patients after steroid tapering did not differ between the 2 groups. • 5 patients on adalimumab group and 17 on placebo suffered from serious side effects

Cantini, et al.	Case series	2001	4 patients with severe GCA.	• 3 infliximab doses (3 mg/kg) at weeks 0, 2 and 6 • 5 mg/day of prednisolone was given in 1st 2 weeks. • After 2nd infliximab infusion if remission is obtained then steroid will be withdrawn, • Then if clinical remission occurred the 3rd infliximab dose will be given	• All 4 patients responded well to Infliximab • After 3rd infusion of infliximab 3 patients are in remission without steroid for 6, 5 and 5 months. • 1 patient relapse after the 2nd infliximab infusion and withdrew from the study.
Andonopoulos AP, et al.	Case series	2003	2 male patients 85 and 80 years old, were seen six months apart from each other. They had typical picture and biopsy of GCA with high acute phase reactant levels. 3 mg/kg of infliximab were given intravenously. The second infusion was given after two weeks with decreasing ESR, and a third, one month later with normal ESR and CRP.	Using infliximab in two patient with GCA, without concomitant administration of corticosteroids.	Patients responded very well after the first infusion, but then patients relapsed in the first months after treatment. The requirement for infliximab is not cost effective to be used on the long run.

BEHÇET'S DISEASE

Behçet's Disease **(BD)** is an inflammatory disorder characterized recurrent oral aphthous ulcer and systemic manifestations include genital ulcer, skin lesion and neurological manifestations [36]. The ability of BD to involve more than one type of vessel makes it unique and remarkable vasculitic disease. Several etiologies have been proposed to play an important role in development of BD [37]. Genetic influences, including association with certain Human Leukocyte Antigens **(HLA)** as well as some non-HLA genes, some bacterial pathogens, associated cytokines and hematopoietic cells, involvement of immune complexes and autoantibodies and finally vascular endothelial activation and hypercoagulability all have been implicated. There is consistent evidence supports the involvement of HLA-B51 gene in the pathogenesis of BD [38]. However, higher rate of streptococcus mutans has been isolated from salivary secretion of 106 Turkey patients BD in comparison to control group suggesting the bacterial involvement in the pathogenesis of the disease [39]. Alteration of T cell function and cellular activation were also observed [37], autoreactive T cells appear to play a critical role in the pathogenesis of BD. This fact provided by a trial of lymphocyte depletion via anti CD-52 antibody CAMPATH 1-H results in reducing disease activity in 18 patients [40]. Importantly, TNF-α as a T cell subpopulation plays a critical role in the disease activation concomitantly with IL-8 and IL-12 [41]. In 24 patients with active uveitis high levels of C3, C4, IL-6, IL-8, and TNF- α were found compared with controls [42]. Clinical manifestations of BD constitute a wide spectrum of symptoms ranging from recurrent

oral ulcers initially, then progressively involve the ocular system in more than two third of the patients, vascular disease in one third of the patients and up to 20% will experience some sort of neurological deficit [43]. Vascular involvement in BD is common in men more than women, with a unique fashion that involves the small, medium and large vessels. Perivascular and endovascular inflammation may lead to hemorrhage, stenosis, and aneurysm formation, thrombus formation in both arteries and veins.

The current therapeutic modalities for BD came from case reports and case series, with few follow-up studies that confirms these case reports and series findings. Currently, for minor disease manifestations that interfere with patients's life but do not threaten major vital organ including arthritis, oral ulcers, genital ulcers and other skin manifestations, for those people a regimen consists of colchicine initially and GC for patients who do not respond well for colchicine therapy [44,45]. For major disease manifestations that threaten the ocular or neurological system; typical regimen consists of high dose of GC (1mg/Kg/day) not exceeding 80 mg/day for patients with posterior uveitis [46], secondary immunosuppressive agent is necessary to halt the progression of acute uveitis, currently AZA is the recommended agent to be used concomitantly with steroid for uveitis [47]. For neurological disease which is either small vessel vasculitis of the central nervous system or parenchymal disease, a regimen of AZA and high dose steroid can be an acceptable approach [48], alternatives for AZA including MMF, MTX and cyclosporine.

The effect of anti TNF-α in BD have been investigated thoroughly, beneficial effect of infliximab, adalimumab, and etanercept was reported [49,50]. 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 with documented improvement of visual acuity [51]. Surprisingly, relapsed uveitis has been reported in 60% of the patients on infliximab therapy especially in the first year, later on a control was made by increasing the topical glucocorticoid dose and shortening the interval of infliximab therapy. Retrospective analysis of 28 patients with moderate to severe intestinal BD, showed 53% of the examined patients maintained the remission after infliximab therapy during the period of follow-up (median duration 30 months) [52]. In a double blind study on BD [53], more patients remained free of oral lesions after etanercept therapy (45% versus 5% in control group), in terms of nodular skin lesion (85% versus 25%) were observed. The trial did not address the effect of etanercept in more serious complications of BD including vascular, ocular and neurological diseases. Benefit of adalimumab have been reported in one case series [54], eleven patients with ocular disease all showed improvement after adalimumab therapy, by four weeks, ten out of eleven patients showed complete resolution of inflammation with steroid sparing effect was documented. However, some patients who failed infliximab therapy might achieve remission on adalimumab, 17 of 69 patients investigated for this purpose [55], Out of those 17 patients only 12 who had achieved improvement on adalimumab therapy. Anti TNF-α can be valuable modality inducing and maintaining remissions with steroid and immunosuppressive sparing effect for patients with severe vascular, ocular, gastrointestinal

BD who failed to achieve remission on conventional therapy, high quality level of evidence is warranted to assist the practicing rheumatologist in their daily clinical decision toward difficult-to-treat cases of BD. (Table 4 summarizes the current available evidence regarding use of anti TNF-α in BD).

Table 4: Summary of the studies that investigate using of TNF blocker in BD.

Author	Study type	Date	Methodology	Used agnet	Outcomes
Takeuchi M, et al. [51]	Prospective analysis	2014	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.	Infliximab	60% relapse in uveitis cases after first year, Control was made in 90% of the cases later on by increasing topical steroid and inflixmab doses.
Lee JH, et al. [52]	retrospective non-controlled review of medical records	2013	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	Infliximab	The clinical response rates at 2, 4, 30, and 54 weeks were 75%, 64.3%, 50%, and 39.1%, respectively.
Cantini F, et al. [56]	Prospective analysis	2012	Single center, prospective, 6-year duration, follow-up study on 50 consecutive patients	Infliximab	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
Melikoglu M, et al. [53]	Double blind, placebo controlled study.	2005	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	Etanercept	More patients remained free of oral ulcers (45 percent versus 5 percent). -More patients remained free of nodular skin lesions (85 versus 25 percent).
Bawazeer A, et al. [54]	Retrospective review of records.	2010	Twenty-one eyes of 11 male patients with ocular Behçet disease received adalimumab therapy.	Adalimumab	Ten out of 11 patients showed complete resolution of inflammation by 4 weeks. The dosage of steroid and immunosupressive drugs were reduced, then stopped in 3 and 6 patients, respictevely.
Olivieri I, et al. [55]	prospective, longitudinal and observational study	2011	data were collected on efficacy and safety of 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.	Adalimumab	Initially 69 treated with infliximab, lack of response or infusion reaction necessities adminstration of adalimumab, out of those 17, nine patients showed sustained remission and 3 patients with good response.

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein Purpura **(HSP)**, also called immunoglobulin A vasculitis **(IgAV)**, characterized by IgA-containing immune complexes that circulate then deposit inducing inflammation to the blood vessels the gastrointestinal tract, the kidneys, the joints, and, rarely, the lungs and the central nervous system [3]. It is the most common form of vasculitis in pediatric age group, is not uncommon to affect adults with total of 10 % of HSP cases are occur adulthood. The diagnosis of HSP **(IgAV)** is usually based upon the clinical manifestations of the disease. The diagnosis is straightforward when the patients present with the classic triad, palpable purpura of the lower extremities and buttocks in patient with neither thrombocytopenic nor in coagulopathic state, arthritis, abdominal pain and renal disease [3]. The most common presentation was palpable purpura in 96% of patients, then arthritis in 61%, and gastrointestinal involvement in 48% and lastly, 32 % of patients developed renal insufficiency [57]. There is no single laboratory investigations capable to diagnose HSP easily. For instance, serum IgA will be positive only in 50 to 70 % of patients. Skin or renal biopsy may be essential in difficult-to-diagnose cases; including cases that mimic HSP presentation especially when purpura with normal platelets count and coagulation profile present, including acute hemorrhagic anemia of infancy, hypersensitivity vasculitis, and other small vasculitides like microscopic polyangiitis **(MPA)**, eosinophilic granulomatosis with polyangiitis **(Churg-Strauss syndrome)** [57]. However, in 1990 a committee of the American College of Rheumatology establishes diagnostic criteria to diagnose IgA vasculitis [58], as follows:

i. Palpable purpura

ii. Age at onset ≤20 years

iii. Acute abdominal pain

iv. Biopsy showing granulocytes in the walls of small arterioles and/or venules

Retrospective study showed a mean interval time of 13.5 months between the first and second episode of HSP [59]. The clinical outcomes of adults with HSP nephritis are worse than in children [60]. The recurrence rate is higher in those with severe disease, and renal involvement. Diagnosis can be challenging sometimes with multiple conditions. When a patient has a recurrent disease, treatment with PRD and cyclophosphamide **(CYC)** are warranted. Rituximab **(RTX)** has been noted to be a successful treatment for severe refractory chronic HSP [61]. Retrospective study reviewed 3 pediatric patients treated with RTX for severe refractory chronic HSP. All three patients responded to 1 or 2 courses of RTX; no serious adverse events were reported [61].

There are no reported cases that demonstrate the benefit of anti-TNF treatment in HSP. On the contrary, there are multiple case reports about anti-TNF induce leukocytoclastic vasculitis or HSP. Food and Drug Administration has recorded 35 cases of leukocytoclastic vasculitis, twenty cases were after receiving etanercept therapy and 15 after administration of infliximab

[62]. There were multiple cases with Ulcerative Colitis **(UC)** treated with infliximab or etanercept then developed IgA vasculitis which resolved after holding the causative drug [63]. Another report described the first case of HSP with an acute kidney injury after 11 month of treatment with etanercept. Discontinuation of the drug led to the complete resolution of the vasculitis and improvement of renal function [64].

Occurrence of IgA vasculitis is less common after adalimumab therapy; but it can still occur as in one case reportof19-year-old male with severe UC who developed small vessel vasculitis 18 months after adalimumab administration with rapid improvement after discontinuation [65]. Overall, HSP is a disease that can resolve spontaneously. Few cases can be treated with an immunosuppressant. The refractory cases can be treated with RTX. The evidence is lacking to support the routine use of anti-TNF-α in IgA vasculitis. On the contrary, HSP disease is described as one of the side effects of anti-TNF-α therapy, early identification of HSP-associated anti TNF-α is a must by observing the clinically apparent purpura, arthritis or arthralgia, abdominal pain and renal impairment, early discontinuation of the offending agent results in favorable outcomes and resolving of vasculitis. (Table 5).

Table 5: Summary of the studies that investigate using of TNF blocker in KD.

Author	Study type	date	Methodology	Used Agent	Outcomes
Burns et al. [66]	Case series	2008	7 Patients failed to respond to the initial IVIG and methylprednisolone.	5 mg/kg infliximab	improvement of coronary arteries aneurysms without adverse effects
Burns JC, et al. [67]	Retrospective study	2013	• 16 cases in **united states** • all of them failed to respond to the 1st line treatment	Infliximab 5mg/kg	• 13 of 16 responded well with no further complications or adverse effect. • CRP in 10 patients decreased after 48 hours on infliximab infusion
Burns JC, et al. [68]	A multi centers Randomize control Trial.	2005	• 24 cases. • 12 cases received 2nd IVIG infusion compared to 12 cases received Infliximab • All failed to respond to the 1st dose of IVIG	Infliximab 5 mg/ kg	• Symptoms subside in 11 of 12 from infliximab group and 8 out of 12 from IVIG group. • 2 out of 4 non-responder in IVIG group had responded to infliximab. • 18 cases developed side effect due to disease itself. • No significant differences in other measures between the 2 drugs. • All considered as safe drugs.

Song MS, et al. [69]	Retrospective study	2004-2008	• 16 cases in **Korea** • all of them received at least 2 doses of IVIG with or without corticosteroid	5-6.6 mg/kg of infliximab	• Complete resolution occurs in 13 cases, • CRP declined in 14 patients who had pre and post infliximab measure. • Infliximab stopped coronary artery dilatation or slowed the rate of its progression. • 1 case experienced acute hepatitis during treatment and later by 4 months developed calculus cholecystitis.
Son MB, et al.	retrospective study	2000 – 2008	20 patients in infliximab group compared to 86 patients who received a second dose of IVIG after classical therapy failure	Infliximab 5mg/kg	• patients who received infliximab had less days of fever and shorten hospitalization days

CRYOGLOBULINEMIC VASCULITIS

Precipitations of blood proteins at temperature lower than 37ºC is referred to as cryoprecipitation. Cryoglobulin **(CG)** is present when the proteins precipitate on both plasma and serum. Strictly speaking, Cryoglobulinemia is a term often used to describe systemic inflammatory syndrome that involves small-to-medium vessels as a result of CG containing immune complex [74]. One of the most commonly used classification system for Cryoglobulinemia is Brouet classification usually based on the involved CG as follows:

Type I - The presence of isolated monoclonal Immunoglobulin (typically IgG or IgM) is the criterion for classification as a type I CG.

Type II - A mixture of polyclonal immunoglobulin in association with a monoclonal immunoglobulin typically IgM or IgA, with Rheumatoid Factor **(RF)** activity defines type II CG. It is usually associated with persistent viral infections, particularly Hepatitis C Virus **(HCV)** and Human Immunodeficiency Virus **(HIV)** infection.

Type III - Mixed CGs consisting of polyclonal immunoglobulin without a monoclonal immunoglobulin component characterize type III CGs. These cases are often secondary to autoimmune disorders. The clinical presentation CG vasculitis is highly variable depending on the type [74]. Conventional treatment of CG vasculitis involves the treatment of underlying cause (if present) as in, hepatitis C virus **(HCV)**-associated cryoglobulinemic vasculitis must be treated first with eradication of the viral load [75]. Patients with severe life- or organ-threatening manifestations of cryoglobulinemic vasculitis may benefit from treatment with RTX [76], while CYC use is reserved for patients with severe disease who are unable to be treated with antiviral or RTX. Adjunctive therapy with plasmapheresis can be used for patients with severe organ- or life-threatening disease.

There is consistent evidence that support the benefit of anti-TNF-α alpha agents in treatment of refractory cases of cryoglobulinemic vasculitis. In an open pilot study of ten patients with different vasculitis, one case was cryoglobulinemic vasculitis, refractory to conventional therapy for which infliximab 5mg/kg was used on days 1, 14, 42 and then every 8 weeks. The treatment response was evaluated clinically with the Birmingham Vasculitis Activity Score 2000 **(BVAS)**. Complete or partial remission was observed in all patients with significant drop in BVAS. The only adverse effect was cutaneous eruption observed in two patients [77]. One case report [78], of 48-year-old woman with a 6 month history of relapsing rash, abdominal pain and peripheral edema who diagnosed with HCV-negative cryoglobulinemic vasculitis with glomerulonephritis and treatment commenced with conventional therapy with no remission, the disease was complicated with intestinal vasculitis and significant gastrointestinal bleeding which necessitate surgical interventions with laparotomy, single dose of infliximab 5mg/kg was administered resulting in complete resolution of the vasculitis-related symptoms; followed by uneventful clinical course [78]. In conclusion anti-TNF-α agents successfully induced prompt symptomatic responses in patients with cryoglobulinemic vasculitis especially patients who are refractory to conventional therapy. However, its rarity strongly limits conduction of large comparative prospective study to investigate the usefulness and safety of anti TNF-α in such cases. (Table 6).

Table 6: Summary of the studies that investigate using of TNF blocker in PAN.

Author	Study type	Date	Methodology	Used Agent		Outcomes
Lara Valor, et al. [79]	Case report	2013	Young male with relapsed cutaneous polyarteritis nodosa after different trials of treatment.	Etanarecept 50 mg/sc Weekly		complete remission after three month. Pt has been followed for 7 years with absolute remission
Maurizio Capuozzo, et al.[80]	Case report	2014	Young male with systemic PAN relapsed on corticosteroid, high doses of CYC and trials of IVIG.	Etanarecept 50 mg/sc Weekly		Clinical response after 2 month . Complete remission after 2 years
Jeffrey Feinstein, et al. [81]	Case repot	2005	Young male with refractory systemic PAN for 9 years despite treatment with corticosteroid, and CYC.	Etanarecept 50 mg/sc Weekly		Remission
Al-Bishri J, et al. [82]	Case report	2005	Young Female diagnosed as a severe (PAN) with visceral involvement. She received high doses of corticosteroid and CYC with no response.	Infleximab 3mg/kg at 0,2,and 6 weeks then every 8 weeks		Remission
Takeshi Zoshima, et al. [83]	Case report	2012	60 year female with cPAN with hep B Received intensive treatment of Prednisolone ,CYC , AZA , Tacrolimus IVIG & plasma exchange	Etanarecept 25 mg/kg sc weekly	lamuvidin 100 mg/day	Remission With no reactivation of hep B
Watanabe K, et al. [84]	Case report	2016	3 year old yong male , PAN with vertebral artery vasculitis . treated with methylprednisolone and CYC.	Tocilizumab 4 mg/kg q 4week		Remission within 7 month.
Seri Y, et al. [85]	Case report	2015	59 male with PAN treatment failed on steroid and CYC	375 mg/m^2 IV infusion Weekly		Remession

HYPOCOMPLEMENTIC VASCULITIS

Hypocomplementemic Urticarial Vasculitis Syndrome **(HUVS)**, or McDuffie syndrome, is a rare disease. Immune complex mediated small vessel vasculitis which present with chronic, nonpruritic, urticarial vasculitic lesions that persist more than 24 hours or recur at short intervals. Debate surrounds the pathophysiology of HUVS; however, low serum complement measurements in patients indicate the activation of the classical pathway, with low C1q, C4, and variably decreased C3 levels [24]. The rarity of the disease contributes to insufficient availability of evidence, and the treatment recommendations are based exclusively on reports of single cases or small series. The treatment of this disorder varies according to the disease extent; Antihistamines represent the cornerstone of treatment for patients who have UV with only cutaneous lesions, serving to control the itching. Antihistamines seldom suffice alone; patients with hypocomplementemia initially almost always require GC therapy. Other immunosuppressive are combined with GC, including MTX, AZA and cyclosporine, CYC, and MMF. In highly active disease; plasmapheresis may play a role to halt the progression. Dapsone has also been used in the treatment of HUVS [33]. But the best strategy for treating HUV has yet to be defined. There were no trials addressed the effectiveness of TNF blockers in the treatment of hypocomplementemic urticarial vasculitis as other vasculitis types. (Table 7).

Table 7: Summary of the studies that investigate using of TNF blocker in HSP.

Author	Study type	Date	Methodology	Used Agent	Outcomes
Donnithorne KJ, et al. [62]	Retrospective analysis	2008	Three Young patient with refractory, chronic Henoch-Schönlein purpura	RTX 375 mg/m2. IV infusion Weekly	Remission after 1-2 dose without serious Side Effects.

KAWASAKI DISEASE

Kawasaki Disease **(KD)** is a multisystem inflammatory disorder associated with medium-sized arteries vasculitis that predominantly affect coronary arteries, making KD the second most common vasculitis in children after HSP and number one cause of children's acquired heart diseases in developed countries [86]. It is a self-limited disease can eventually progress to Coronary Artery Aneurysm **(CAA)** if left untreated in 25% of the cases [87].

The etiology of the disease remains unclear and poorly understood; recent studies suggest some infectious triggers it in a genetic predisposed individual, with no single agent found [88].

TNF alpha inflammatory mediator plays a major role in disease pathology. In mice the affected vessels showed TNF alpha and IFN, while TNF alpha was absent in spared vessels [88,89]. In human serum; TNF alpha is markedly elevated in KD patients CAA [90].

Current therapeutic regimen for patients with KD who present acutely consists of early administration of intravenous immunoglobulin **(IVIG)** with high dose aspirin [86,91], within 10

days of fever onset IVIG dose 2g/kg as single infusion over 12 hours then low dose of aspirin and follow up until echocardiograms is normal. Early recognition and treatment with IVIG and aspirin based on clinical trials and meta-analysis has shown to reduce the incidence of CAA [90].

Most of the patients responded well to the standard regimen with marked clinical response within 48 hours of IVIG infusion. Approximately 15% - 25% of children are IVIG resistant and failed to respond upon initial treatment and continued to have difficult-to-treat KD [69,92].

Adding 2 mg/kg/day methylprednisolone in recent Japanese randomized controlled trial showed significant decrease in coronary artery adverse outcome [87]. Another trial in USA showed no beneficial effect of methylprednisolone addition to conventional regimen [86].

There are two anti TNF alpha agents have been investigated in treatment of KD, infliximab and etanercept [91, 89]. Several studies showed the effectiveness of Infliximab in refractory KD [93], one dose of infliximab (5 mg/kg / day) in 7 patients who failed to achieve remission on conventional therapy of KD showed improvement of CAA without adverse effects [71]. A study in 2004 showed good response of two patients on infliximab therapy after the relapsing course on conventional therapy [68]. In 2005, a retrospective analysis of 16 cases from USA, all patients failed to achieve remission on conventional therapy, 13 of 16 responded well after single infusion of infliximab with no adverse reaction. C-reactive protein in 10 patients initially elevated then subsided after 48 hours on infliximab therapy [67]. In a period from 2004 - 2006 a multi centric randomize control trial compared the usage of second IVIG infusion versus Infliximab in children who failed to respond to the initial dose of IVIG [94], symptomatic relieve was observed in 11 out of 12 on infliximab group and 8 out of 12 on IVIG group, 2 out of 4 non-responder in IVIG group had responded to infliximab. Side effects due to disease itself developed in 18 cases, transient hepatomegaly noted in 10 of them were not attributed to KD, and couldn't be ruled out before treatment. Those 10 patient were as following (5 were treated with infliximab, 1 with IVIG, 3 with IVIG followed by infliximab, and 1 with infliximab followed by IVIG), all of cases were resolved spontaneously by first or second visits. This study concluded that infliximab is not inferior to IVIG therapy in patients who fail to achieve remission after initial IVIG administration [94]. In 2004 - 2008 a retrospective multi centers study of 16 cases in Korea were conducted, all of the enrolled patients have refractory KD who received at least two doses of IVIG with or without corticosteroid. Complete resolution occurs in 13 cases, in the 3 who failed to respond; one case responded to the fourth dose of IVIG, another case responded after adding IV corticosteroid, the third case; relapsed after tapering of the steroid dose. Two cases achieved permanent resolution of arthritis upon follow-up. CRP declined in all 14 patients who had pre and post infliximab measure, coronary artery lesions found in 15 out of 16 patients before infliximab, the final result after infliximab therapy is significant improvement in terms of coronary artery disease by slowing the rate of progression. No infusion reactions or complications were noted in all patients except in 1 case who experienced acute hepatitis during treatment and later by 4 months developed

calculus cholecystitis [92]. Several case reports with similar finding were reported [69,95]. In Japan an open label case series of 20 patients refractory to IVIG therapy treated with Infliximab, 18 of them had rapid symptomatic improvement, inflammatory mediators and normalization of dilated coronary artery after 1 month of infliximab administration. No adverse effects or infusion reaction were observed in these patients [96]. Another retrospective studies found that patients who received infliximab compared to patients who received a second dose of IVIG had less days of fever and shorten hospitalization days [71]. A randomized controlled trial in 2016 [73], compared a group of 32 KD patients who received second dose of IVIG and group of 11 KD patients who received infliximab. The infliximab group showed better response as 10 patients (90.9%) had shorter duration of fever and fewer days of hospitalization comparing to 21 (65.6%) in the IVIG group. Coronary artery outcomes and adverse events were similar [73].

Phase 3 randomized, double-blind, placebo-controlled trial was conducted to address the effect of adding Infliximab to the standard therapy [72], ninety eight patients in Infliximab group and 98 in placebo group, patients in Infliximab group had less days with fever, greater reduction in inflammatory mediators, no infusion reaction to IVIG compared with 13.4% in Placebo group, but the infliximab addition did not reduce primary treatment resistance in KD [72].

Concerns regarding adverse effect of Infliximab on the immune system was addressed through a double blinded Phase III randomized clinical trial, the study involved addition of Infliximab to the standard IVIG therapy in 14 patients [71], seven patients were treated with IVIG alone and another 7 received IVIG plus infliximab, it was found that the treatment with Infliximab does not affect the immunological cells that were studied in an adverse way [71].

Another investigated anti TNF alpha agent in treatment of refractory KD is etanercept, few studies have examined its efficacy and safety in KD, a prospective open label trial of 17 patients of KD with fever less than 10 days who received the conventional regimen, received etanercept immediately after IVIG infusion and then weekly. For the initial safety evaluation, the first 5 patients received 0.4 mg/kg/dose; subsequent subjects received 0.8 mg/kg/dose. 15 patients completed the study. No serious adverse events related to etanercept occurred. No patient demonstrated prolonged fever or cardiac complications [96]. Case report of 20 month old girl who was diagnosed with KD did not respond to conventional therapy with two doses of IVIG and methylprednisone [97]. Her CAA progressed with sustainable high grade fever, she received one dose of etanercept 0.4mg/kg/dose subcutaneously on day 17, fever subsided with no further relapses occurred with documented improvement of CAA, no side effects were noted during hospitalization [96].

Etanercept initial results are more promising than infliximab; however more clinical trials are needed to reach a conclusion. Using of anti-TNF alpha in refractory KD in patients who did not respond to the conventional regimen is effective in inducing and maintaining the remissions of the disease without serious adverse effects. (Table 8).

Table 8: Summary of the studies that investigate using of TNF blocker in ANCA vasculitis.

Author	Study Type	Date	Methodology	Used Agent	Outcome
Bartolucci P, et al. [98]	Prospective study	2002	10 pt with different vasculitis, 7 pt had GPA with active disease or new flare despite conventional therapy.	Infliximab 5mg/kg at day1, 14, 42, and q8 wks. Evaluated by BVAS score.	Complete or partial remission within 2 months. No major side-effects were observed. A mild transient cutaneous eruption was observed only after the first anti-TNF-α Ab infusion in one patient, for whom anti-TNF-α Ab was discontinued. No infection was noted.
Lamprecht P, et al. [99]	Prospective study	2002	6 pt with GPA refractory to standard treatment with cyclophosphamide and corticosteroid.	Infliximab (3 mg/kg in two patients and 5 mg/kg in four patients) with a 2-week interval after the first administration. Evaluated by BVAS score. A standardized interdisciplinary approach was used for the follow-up of specific organ involvement.	One patient was withdrawn because of suspected systemic infection
Booth A, et al. [100]	Prospective study	2002	6 pt (3 with GPA and 3 with MPA) refractory to standard treatment.	Infliximab 200 mg IV /month for three months. Evaluated by BVAS score.	5 patients had remission, with steroid withdrawal or dose reduction by more than 50%. 1 patient developed fatigue, myalgia and blured vision within 24 h after 1st infusion ich did not recur. 1 patient developed relapse. (BVAS) improved. ESR, CRP dropped. ANCA status unchanged.
Morgan M, etal. [101]	Cohort study	2010	33 patients with active AAV .recived standard therapy or additional infliximab . Follow-up was for 12 months	17 pt were treated with standard therapy. 16 pt were treated with standard therapy + infliximab at weeks 0, 2, 6 and 10.	The addition of infliximab to standard therapy did not influence remission rates, adverse events, damage index scores, relapse rates or biomarker levels

De Menthon M, et al. [102]	Prospective study	2011	Patients with systemic GPA refractory to, or intolerant to steroids and consecutive immunosuppressant lines. Between June 2004 and June 2007, 17 patients were randomly assigned to receive either infliximab or rituximab, in addition to CS and immunosupressant. (8 were given rituximab and 9 received infliximab)	The initial IV dose of infliximab (3 mg/ kg) was administered IV on days 1 and 14, and response was assessed on day 42 Rituximab was given IV (0.375g/m2) on days 1, 8, 15 and 22. Evaluated by BVAS score.	Complement remission (2 infliximab pt, 4 rituximbpt) Partial remission (1 infliximab pt, 1 rituximbpt) Failure (5 infliximab pt, 2 rituximbpt) Relapse (2 infliximab pt, 1 rituximbpt) 2 deaths.
Stone J H, et al. [103]	Prospective study	2001	20 patients with persistently active disease or with new flares of previously established GPA.	etanercept (25 mg subcutaneously twice weekly BVAS used for assessment. 6-month follow up.	16 patient dropped BVAS to zero. 15 patient had intermittent active GPA. NO deaths. 5 patient had injection site reaction. 1 patient developed pneumococcal tracheobronchitis and subsequently had a localized Herpes zoster infection
WEGT research group. [104]	RCT	2005	Conducted a randomized, placebo-controlled trial at eight centers to evaluate etanercept for the maintenance of remission in 180 patients with GPA.	Etanercept versus placebo. BVAS used for assessment. Follow-up for 27 months.	no significant differences between the etanercept and control groups in the rates of sustained remission (69.7 percent vs. 75.3 percent, P=0.39 118 flares in the etanercept group and 134 in the control group During the study, 56.2 percent of patients in the etanercept group and 57.1 percent of those in the control group had at least one severe or life-threatening adverse event or died. Solid cancers developed in 6 patients in the etanercept group, as compared with none in the control group.

| Laurino S, et al. [105] | Prospective study | 2010 | 14 patients with acute flares of AAV (9 GPA , 5 MPA) either as first manifestation of disease or relapse. | Adalimumab (40 mg s.c.) was given every 2 weeks for 3 months, in combination with intravenous cyclophosphamide and a reducing course of prednisolone. Evaluated by BVAS score. | 11 patient had remission within 2 weeks. BVAS score decreased, prednisolone dose decreased, eGFR raised. 3 patients got infection. 1 patient died. |

POLYARTERITISNODOSA

Polyarteritisnodosa **(PAN)** was first described by Kussmaul and Maier in 1866as a systemic necrotizing vasculitis that typically affects medium-sized muscular arteries, with occasional involvement of small muscular arteries [106]. Importantly, PAN does not cause high levels of Anti Neutrophil Cytoplasmic Antibodies **(ANCA)**. PAN usually resulting in microaneurysms, hemorrhage, organ ischemia, and infarctions [107]. PAN is a rare entity with an estimated annual incidence of 2.0-9.0/million in adults and appears more common in men with a male to female ratio of 2:1 [108]. Typically, the onset of the disease is between the ages of 25 and 50 years and is predominantly observed in patients aged 45 to 65 years [109]. In spite of the fact that the underlying cause of pathogenic PAN is still unknown, it seems that cytokines play a role by altering some vascular tissue cell functions. There was a retrospective study raised the important role of cytokines in active disease and studied cytokines reduction after treatment [110]. Pathological examination of the involved vessels usually revealed segmental transmural inflammation of muscular arteries, the cellular infiltrate contains polymorphonuclear leukocytes and mononuclear cells. Fragments of white blood cells (leukocytoclasis) may be noted [111]. Patients with polyarteritis nodosa PAN typically present with systemic symptoms (fatigue, weight loss, weakness, fever, arthralgias) and signs (skin lesions, hypertension, renal insufficiency, neurologic dysfunction, abdominal pain). Skin manifestations of PAN may include tender erythematous nodules, purpura, livedo reticularis, ulcers, and bullous or vesicular eruption [112]. Renal disease is also reported as a manifestation of PAN in autopsy studies, the kidneys are the most commonly involved organ. Renal involvement frequently leads to variable degrees of renal insufficiency and hypertension [112]. A mononeuropathy multiplex (or asymmetric polyneuropathy) affecting named nerves (eg, radial, ulnar, peroneal), typically with both motor and sensory deficits, is one of the most common findings in patients with PAN, occurring in up to 70 percent of patients [113]. Hepatitis B is one of the identified causes of PAN but the exact underlying etiology still remains unclear [107]. There is no single laboratory test for PAN. Basic work up it might help to ascertain the extension of the disease and the degree of involvement. Basic work up including serum creatinine, muscle enzyme concentrations, liver function studies, hepatitis **(HBV and HCV)** serologies, and urinalysis. Because of the rarity of this disease and adverse effects related to the treatment, we prefer a biopsy-based diagnosis whenever possible to avoid the unnecessarily therapeutic interventions.

Diagnosis of PAN is based on **(ACR)** 1990 criteria but diagnosis should ideally be confirmed by biopsy of a clinically affected organ [110]. The treatment and the prognosis are highly variable, depend if the disease is systematic or localized only to the skin. In concept, treatment of PAN consists of induction therapy and maintenance therapy.

Induction therapy is the combination of corticosteroids and CYC for 2 to 4 months. When remission is achieved, maintenance therapy can be in the form of either AZA (2 mg/kg/day) or MMF (1 g twice a day) for 18-48 months. Plasma exchange is reserved for refractory cases. Despite of aggressive medical management with corticosteroids and CYC, many patients develop aggressive disease refractory to all available modalities with high incidence of mortality reaching 22.4% within five years from the onset of the disease, and of the survivors, medication-related adverse effects are frequently reported [114].

Two anti-TNF biologics have been proposed in the management of PAN, etanercept and infliximab. There were six cases found in the literature that showed examples of the use of biologic agents after failure to achieve remission on conventional therapy [79-82,84,85]. The selected cases cover a wide spectrum of clinical presentation and represent different age groups. In each case, patient was treated with one or a combination of corticosteroids and immunosuppressant with little or no response to treatment. Four cases were treated with etanercept [79,80,81] one with infliximab [82], one with tocilizumab [84], and one rituximab [85]. All cases showed a good response to treatment and achievement of remission on clinical and biochemical basis with no serious side effects.

Although, we found no prospective studies or large trials address the role of anti-TNF to induce or maintain remission in patients with PAN, there are several case reports that suggest the benefits of anti-TNF-alpha in severe and refractory cases. Considering the high mortality, high morbidity and the observant resistance for immunosuppressant, there is a growing importance and great need for more effective therapeutic modalities that can be substitute immunosuppressant and at the same time can affect the progression of the disease. In conclusion the safety and efficacy of anti TNF-α in PAN is not well-studied, more case-control studies are required to reach a solid evidence for routine use of these agents. (Table 9).

Table 9: Summary of the studies that investigate using of TNF blocker in Cryoglobulinemic vasculitis.

Author	Study type	date	Methodology	Exposure	outcomes
Bartolucci P, et al. [112]	Prospective study	2002	10 pt with different vasculitis, one case had cryoglobulinemic vasculitis, with active disease or new flare despite conventional therapy.	Infliximab 5mg/kg at day1, 14, 42, and q8 wks. Evaluated by BVAS score.	Symptomatic improvement. No side effect.
Koukoulaki M, et al. [78]	Case report	2005	Young women k/c hepatitis C negative cryoglobulinemic vasculitis on conventional therapy developed intestinal vasculitis and significant GI bleeding	Single dose of Infliximab 5mg/kg	Stabilization of pt bleeding and HB level and discharge home.

ANCA ASSOCIATED VASCULITIS

ANCA Associated Vasculitides **(AAV)** are group of conditions characterized by inflammation and necrosis of small and medium-sized blood vessels [3]. These include Microscopic polyangiitis **(MPO)**, granulomatosis with polyangitis **(GPA)**, and eosinophilic granulomatosis with polyangitis **(EGPO)**, all these disorders share pathogenic, pathological, and clinical features. They all involve capillaries, venules, arterioles, and small arteries. Approximately 90% of patients have autoantibodies either to myeloperoxidase **(MPO-ANCA)** or to proteinase 3 **(PR3-ANCA)**. The clinical presentations of these vasculitic disorders are variable. it can be limited to the kidney alone, or may involve the upper respiratory tract, the lungs, the skin, or a number of other organs in various combinations [115].

Combined corticosteroid and cyclophosphamide therapy remains the standard of care for anti neutrophil cytoplasmic antibody **(ANCA)**-associated vasculitides. Current AAV treatment is based on a six-month induction phase with high-dose steroids and Cyclophosphamide [116,117] followed by an 18-month maintenance therapy with either azathioprine or methotrexate [117,118]. MMF in combination with prednisolone can induce remission in patients with relapses of AAV intolerant to cyclophosphamide [119]. Rituximab is the most promising agent, many evidence demonstrated that rituximab is not inferior to cyclophosphamide in inducing remission [120,121] also, rituximab can be used as maintenance therapy [122,123]. Treatment with plasma exchange should also be considered in patients with AAV and acute kidney injury manifested as (Creatinine >500 μmol/l) or life-threatening pulmonary hemorrhage [124]. Anti-TNFα therapy consider a new wave of specifically targeted biological interventions of significant role in the treatment of vasculitis. It grants the chance of improved therapeutic efficacy over conventional options and the achievement of reducing exposure to steroids and immunosuppressive drugs. To confirm these observations further studies are needed [103] (See Table 4).

In one study of ten patients with different forms of ANCA associated vasculitis, seven of them had GPA. They received infliximab therapy (5 mg/kg) on days 1, 14, 42 and then every 8 weeks.

Complete or partial remission was observed in all patients with mild cutaneous eruption was observed only in one patient [98].

Interstingly, one cohort study of 33 patients with active ANCA associated vasculitis conclude the addition of infliximab to standard therapy did not show clinical benefit [102], this conclusion supports the negative trials on effective use of TNF blocker in AAV.

Multicentric prospective randomized control trial involving 17 patients compared the efficacy of infliximab or rituximab in association with steroids and immunosuppressive drugs in refractory GPA, showed the efficacy of infliximab and/or rituximab to achieve remission at one year follow-up [101].

Another anti TNF therapy, etanercept was investigated in an open label trial including 20 patients with relapsing or incompletely controlled GPA and seemed efficient with a 3-point reduction of the Birmingham Vasculitis activating **(BVAS)** score at 6 months, However, relapsing disease was observed even on etanercept therapy during follow-up [103]. Larger controlled prospective study including 180 GPA patients showed etanercept therapy is not effective in maintaining the remission in GPA. However, it should be noted that this study has some design limitations since the two groups were not equally matching each other at the baseline, and some patients had localized forms of the disease. WGET study provides data confirming that the addition of etanercept to the conventional therapy is ineffective in the maintenance remission of GPA. Durable remissions were achieved in only a minority of the patients, and there was a high rate of treatment-related complications [104].

Adding adalimumab therapy to prednisolone and cyclophosphamide for the treatment of severe AAV was conducted on 14 patients. No significant benefit was achieved in terms of clinical and biochemical response, although, a significant steroid sparing effect was noted [105].

References

1. Roane DW, Griger DR. An approach to diagnosis and initial management of systemic vasculitis. Am Fam Physician. 1999; 60: 1421-1430.

2. Little MA, Nightingale P, Verburgh CA, Hauser T, De Groot K, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis. 2010; 69: 1036-1043.

3. Jennette JC1, Falk RJ, Bacon PA, Basu N, Cid MC, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013; 65: 1-11.

4. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010; 363: 221-232.

5. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010; 363: 211-220.

6. Beutler B, Cerami A. Cachectin: more than a tumor necrosis factor. N Engl J Med. 1987; 316: 379-385.

7. Vassalli P. The pathophysiology of tumor necrosis factors. Annu Rev Immunol. 1992; 10: 411-452.

8. Aries PM, Lamprecht P, Gross WL. Biological therapies: new treatment options for ANCA-associated vasculitis? Expert Opin Biol Ther. 2007; 7: 521-533.

9. Niti Goel, Sue Stephens. Certolizumab pegol. MAbs. 2010; 2: 137-147.

10. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009; 374: 210-21.

11. Buonuomo PS, Bracaglia C, Campana A, Insalaco A, Pardeo M, et al. Infliximab therapy in pediatric Takayasu's arteritis: report of two cases. Rheumatol Int. 2011; 31: 93-95.

12. Schneeweiss S, Setoguchi S, Weinblatt ME, Katz JN, Avorn J, et al. Anti-tumor necrosis factor a therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum. 2007; 56: 1754-1764.

13. Pallavicini FB, Caporali R, Sarzi-Puttini P, Atzeni F, Bazzani C, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev. 2010; 9: 175-180.

14. Zink A, Askling J, Dixon WG, Klareskog L, Silman AJ, et al. European biologicals registers: methodology, selected results and perspectives. Ann Rheum Dis. 2009; 68: 1240-1246.

15. Pariser KM. Takayasu's arteritis. Curr Opin Cardiol. 1994; 9: 575-580.

16. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, et al. Takayasu arteritis. Ann Intern Med. 1994; 120: 919-929.

17. Hoffman GS, Merkel PA, Brasington RD, Lenschow DJ and Liang P. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. Arthritis & Rheumatism. 2004; 50: 2296-2304.

18. Katoh N, Kubota M, Shimojima Y, Ishii W, Matsuda M, et al. Takayasu's arteritis in a patient with Crohn's disease: anunexpected association during infliximab therapy. Intern. Med. 2010; 49: 179-182.

19. Comarmond C, Plaisier E, Dahan K, Mirault T, Emmerich J, et al. Anti TNF-Î± in refractory Takayasu's arteritis: cases series and review of the literature. Autoimmun Rev. 2012; 11: 678-684.

20. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum. 1990; 33: 1129-1134.

21. Vinicki JP, García-Vicuña R, Arredondo M, López-Bote JP, García-Vadillo JA, et al. "Sustained remission after long-term biological therapy in patients with large vessel vasculitis: an analysis of ten cases". Reumatología Clínica. 2016.

22. Ca˜nas CA, Ca˜nas F, Izquierdo JH, Echeverri AF, Mejía M, et al. Efficacy and safety of anti-interleukin 6 receptor monoclonal antibody(tocilizumab) in Colombian patients with Takayasu arteritis. J Clin Rheumatol. 2014; 20: 125-129.

23. Goel R, Danda D, Kumar S, Joseph G . Rapid control of disease activity by tocilizumab in 10 'difficult-to-treat' cases of Takayasu arteritis. Int J Rheum Dis. 2013; 16: 754-761.

24. Abisror N, Mekinian A, Lavigne C, Vandenhende MA, Soussan M, et al. Club Rhumatismes et Inflammation, and SNFMI. Tocilizumab in refractory Takayasu arteritis: a case series and updated literature review. Autoimmun Rev. 2013; 12: 1143-1149.

25. Nakaoka Y, Higuchi K, Arita Y, Otsuki M, Yamamoto K, et al. Tocilizumab for the treatment of patients with refractory Takayasu arteritis. Int Heart J. 2013; 54: 405-411.

26. Nunes G, Neves FS, Melo FM, de Castro GR, Zimmermann AF, et al. Takayasu arteritis: anti-TNF therapy in a Brazilian setting. Rev Bras Reumatol. 2010; 50: 291-298.

27. Hernandez-Rodriguez J, Segarra M, Vilardell C, Sánchez M, García-Martínez A, et al. "Tissue production of pro-inflammatory cytokines (IL-1ß, TNFa and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis". Rheumatology. 2004; 43: 294-301.

28. Henderson CF, Seo P. Biologic agents in systemic vasculitis. Int J Clin Rheumtol. 2011; 6: 453-462.

29. Dasgupta B, et al. "BSR and BHPR guidelines for the management of giant cell arteritis". Rheumatology: 2010

30. Dasgupta B; Giant Cell Arteritis Guideline Development Group. Concise guidance: diagnosis and management of giant cell arteritis. Clin Med (Lond). 2010; 10: 381-386.

31. Airo P, Antonioli CM, Vianelli M, Toniati P. "Anti-tumour necrosis factor treatment with infliximab in a case of giant cell arteritis resistant to steroid and immunosuppressive drugs". Rheumatology. 2002; 41: 347-349.

32. Ahmed MM, Mubashir E, Hayat S, Fowler M, Berney SM. Treatment of refractory temporal arteritis with adalimumab. Clin Rheumatol. 2007; 26: 1353-1355.

33. Barraclough K, Mallen CD, Helliwell T, Hider SL, Dasgupta B. Diagnosis and management of giant cell arteritis. Br J Gen Pract. 2012; 62: 329-330.

34. Guida A, Tufano A, Perna P, Moscato P, De Donato MT, et al. The thromboembolic risk in giant cell arteritis: a critical review of the literature. Int J Rheumatol. 2014; 2014: 806402.

35. Osman M, Pagnoux C, Dryden DM, Storie D, Yacyshyn E. The role of biological agents in the management of large vessel vasculitis (LVV): a systematic review and meta-analysis. PLoS One. 2014; 9: e115026.

36. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's Disease. N Engl J Med 1999; 341:1284-1291.

37. Direskeneli H. Behçet's disease: infectious aetiology, new autoantigens, and HLA-B51. Ann Rheum Dis. 2001; 60: 996-1002.

38. De MENTHON, MATHILDE et al. "HLA–B51/B5 and the Risk of Behçet's Disease: A Systematic Review and Meta-Analysis of Case–Control Genetic Association Studies". Arthritis and rheumatism. 2009; 61: 1287-1296.

39. Mumcu G, Inanc N, Aydin SZ, Ergun T, Direskeneli H . Association of salivary S. mutans colonisation and mannose-binding lectin deficiency with gender in Behçet's disease. Clin Exp Rheumatol. 2009; 27: S32-36.

40. Lockwood CM, Hale G, Waldman H, Jayne DR. Remission induction in Behçet's disease following lymphocyte depletion by the anti-CD52 antibody CAMPATH 1-H. Rheumatology (Oxford). 2003; 42: 1539-1544.

41. Turan B, Pfister K, Diener PA, Hell M, Möller B, et al. Soluble tumour necrosis factor receptors sTNFR1 and sTNFR2 are produced at sites of inflammation and are markers of arthritis activity in Behçet's disease.Scand J Rheumatol. 2008; 37: 135.

42. Bardak Y, Aridogan BC. The demonstration of serum interleukin 6-8, tumor necrosis factor-alpha, complement, and immunoglobulin levels in Behçet's disease with ocular involvement, Ocul Immunol Inflamm. 2004; 12: 53.

43. Zouboulis CC, Vaiopoulos G, Marcomichelakis N, Palimeris G, Markidou I, et al. Onset signs, clinical course, prognosis, treatment and outcome of adult patients with Adamantiades-Behçet's disease in Greece.Clin Exp Rheumatol. 2003; 21: S19.

44. Yurdakul S, Mat C, Tüzün Y, Ozyazgan Y, Hamuryudan V, et al. A double-blind trial of colchicine in Behçet's syndrome. Arthritis Rheum. 2001; 44: 2686-2692.

45. Saenz A, Ausejo M, Shea B, Wells G, Welch V, et al. Pharmacotherapy for Behcet's syndrome. Cochrane Database Syst Rev. 2000; 2: CD001084.

46. Reed JB, Morse LS, Schwab IR. High-dose intravenous pulse methylprednisolone hemisuccinate in acute Behçet retinitis. Am J Ophthalmol. 1998; 125: 409-411.

47. Hatemi G, Silman A, Bang D, Bodaghi B, Chamberlain AM, et al. EULAR recommendations for the management of Behçet disease. Ann Rheum Dis. 2008; 67: 1656-1662.

48. Kalra S, Silman A, Akman-Demir G, Bohlega S, Borhani-Haghighi A, et al. Diagnosis and management of Neuro-Behçet's disease: international consensus recommendations. J Neurol. 2014; 261: 1662-1676.

49. Sfikakis PP, Markomichelakis N, Alpsoy E, Assaad-Khalil S, Bodaghi B, et al. Anti-TNF therapy in the management of Behcet's disease--review and basis for recommendations. Rheumatology (Oxford). 2007; 46: 736-741.

50. Arida A, Fragiadaki K, Giavri E, Sfikakis PP. Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. Semin Arthritis Rheum. 2011; 41: 61-70.

51. Takeuchi M, Kezuka T, Sugita S, Keino H, Namba K, et al. Evaluation of the long-term efficacy and safety of infliximab treatment for uveitis in Behçet's disease: a multicenter study. Ophthalmology. 2014; 121: 1877-1884.

52. Lee JH, Cheon JH, Jeon SW, Ye BD, Yang SK, et al. Efficacy of infliximab in intestinal Behçet's disease: a Korean multicenter retrospective study. Inflamm Bowel Dis. 2013; 19: 1833-1838.

53. Melikoglu M, Fresko I, Mat C, Ozyazgan Y, Gogus F, et al. Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study. J Rheumatol. 2005; 32: 98-105.

54. Bawazeer A, Raffa LH, Nizamuddin SH. Clinical experience with adalimumab in the treatment of ocular Behçet disease. Ocul Immunol Inflamm. 2010; 18: 226-232.

55. Olivieri I, Leccese P, D'Angelo S, Padula A, Nigro A, et al. Efficacy of adalimumab in patients with Behçet's disease unsuccessfully treated with infliximab. Clin Exp Rheumatol. 2011; 29: S54-57.

56. Cantini F, Niccoli L, Nannini C, Kaloudi O, Cassarà E, et al, Efficacy of infliximab in refractory Behçet's disease-associated and idiopathic posterior segment uveitis: a prospective, follow-up study of 50 patients.Biologics. 2012; 6: 5-12.

57. Piram M, Mahr A. Epidemiology of immunoglobulin A vasculitis (Henoch-Schönlein): current state of knowledge. Curr Opin Rheumatol. 2013; 25: 171-178.

58. Mills JA, Michel BA, Bloch DA. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. Arthritis Rheum. 1990; 33: 1114.

59. McCarthy HJ, Tizard EJ. Clinical practice: Diagnosis and management of Henoch-Schönlein purpura. Eur J Pediatr. 2010; 169: 643-650.

---

60. Prais D, Amir J, Nussinovitch M. Recurrent Henoch-Schonlein purpura in children. Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases. 2007; 13: 25-28.

61. Coppo R, Andrulli S, Amore A, Gianoglio B, Conti G, et al. Predictors of outcome in Henoch-Schonlein nephritis in children and adults. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2006; 47: 993-1003.

62. Donnithorne KJ, Atkinson TP, Hinze CH, Nogueira JB, Saeed SA, et al. Rituximab therapy for severe refractory chronic Henoch-Schönlein purpura. J Pediatr. 2009; 155: 136-139.

63. Lee A, Kasama R, Evangelisto A, Elfenbein B, Falasca G . Henoch-Schönlein purpura after etanercept therapy for psoriasis. J Clin Rheumatol. 2006; 12: 249-251.

64. Nishikawa J, Hosokawa A, Akashi M, Mihara H, Nanjo S, et al. [IgA vasculitis associated with anti-TNF-alpha inhibitors in a patient with Crohn's disease]. Nihon Shokakibyo Gakkai zasshi = The Japanese journal of gastro-enterology. 2015; 112: 1852-1857.

65. Rahman FZ, Takhar GK, Roy O, Shepherd A, Bloom SL, et al. Henoch-Schönlein purpura complicating adalimumab therapy for Crohn's disease. World Journal of Gastrointestinal Pharmacology and Therapeutics. 2010; 1: 119-122.

66. Sonoda K, Mori M, Hokosaki T, Yokota S. Infliximab plus plasma exchange rescue therapy in Kawasaki disease. J Pediatr. 2014; 164: 1128-1132.

67. Burns JC, Best BM, Mejias A, Mahony L, Fixler DE, et al. "Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease". The Journal of pediatrics. 2008; 153: 833-838.

68. Burns JC, Mason WH, Hauger SB, Janai H, Bastian JF, et al. "Infliximab treatment for refractory Kawasaki syndrome". The Journal of pediatrics. 2005; 146: 662-667.

69. Song MS, Lee SB, Sohn S, Oh JH, Yoon KL, et al. Infliximab treatment for refractory kawasaki disease in korean children. Korean Circ J. 2010; 40: 334-338.

70. Mori M, Imagawa T, Hara R, Kikuchi M, Hara T, et al. "Efficacy and limitation of infliximab treatment for children with Kawasaki disease intractable to intravenous immunoglobulin therapy: report of an open-label case series". The Journal of rheumatology. 2012; 39: 864-867.

71. Burns J, Song Y, Bujold M, Shimizu C, Kanegaye JT, et al. "Immune-monitoring in Kawasaki disease patients treated with infliximab and intravenous immunoglobulin". Clinical & Experimental Immunology. 2013; 174: 337-344.

72. Tremoulet AH, Jain S, Jaggi P, Jimenez-Fernandez S, Pancheri JM, et al. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet. 2014; 383: 1731-1738.

73. Youn Y, Kim J, Hong YM, Sohn S. "Infliximab as the first retreatment in patients with Kawasaki disease resistant to initial intravenous immunoglobulin". The Pediatric infectious disease journal. 2016; 35: 457-459.

74. Lerner AB, Watson CJ. Studies of cryoglobulins; unusual purpura associated with the presence of a high concentration of cryoglobulin (cold precipitable serum globulin). Am J Med Sci. 1947; 214: 410.

75. Goglin S, Chung SA."Current Treatment of Cryoglobulinemic Vasculitis". Current Treatment Options in Rheumatology. 2016; 2: 213-224.

76. De Vita S, Quartuccio L, Isola M, Mazzaro C, Scaini P, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. Arthritis Rheum. 2012; 64: 843-853.

77. Bartolucci, P, Ramanoelina J, Cohen P, Mahr A, Godmer P, et al. "Efficacy of the anti-TNF-a antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients". Rheumatology. 2002; 41: 1126-1132.

78. Koukoulaki M, et al. "Remission of refractory hepatitis C-negative cryoglobulinaemic vasculitis after rituximab and infliximab". Nephrology Dialysis Transplantation. 2005; 20: 213-216.

79. Valor L, Monteagudo I, de la Torre I, Fernández CG, Montoro M, et al. Young male patient diagnosed with cutaneous polyarteritis nodosa successfully treated with etanercept. Modern Rheumatology. 2014; 24: 688-689.

80. Capuozzo M, Ottaiano A, Nava E, Cascone S, Fico R, et al. Etanercept induces remission of polyarteritis nodosa: a case report. Front Pharmacol. 2014; 5: 122.

81. Feinstein J, Arroyo R. Successful treatment of childhood onset refractory polyarteritis nodosa with tumor necrosis factor alpha blockade. Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases. 2005; 11: 219-22.

82. Al-Bishri J, le Riche N, Pope JE. Refractory polyarteritis nodosa successfully treated with infliximab. J Rheumatol. 2005; 32: 1371-1373.

83. Zoshima T, Matsumura M, Suzuki Y, Kakuchi Y, Mizushima I, et al. A case of refractory cutaneous poly arteritis nodosa in a patient with hepatitis B carrier status successfully treated with tumor necrosis factor alpha blockade. Mod Rheumatol. 2013; 23: 1029.

84. Watanabe K, Rajderkar DA, Modica RF. A Case of Polyarteritis Nodosa Associated with Vertebral Artery Vasculitis Treated Successfully with Tocilizumab and Cyclophosphamide. Case Reports in Pediatrics. 2016; 2016: 7987081.

85. Seri Y, Shoda H, Hanata N, Nagafuchi Y, Sumitomo S, et al. A case of refractory polyarteritis nodosa successfully treated with rituximab. Modern rheumatology / the Japan Rheumatism Association. 2015:1-3.

86. Rowley AH, Shulman ST. Pathogenesis and management of Kawasaki disease. Expert Rev Anti Infect Ther. 2010; 8: 197-203.

87. Jamieson N, Singh-Grewal D. Kawasaki Disease: A Clinician's Update. Int J Pediatr. 2013; 2013: 645391.

88. Yeung RS. Kawasaki disease: update on pathogenesis. Curr Opin Rheumatol. 2010; 22: 551-560.

89. Tacke CE, Burgner D, Kuipers IM, Kuijpers TW. Management of acute and refractory Kawasaki disease. Expert Rev Anti Infect Ther. 2012; 10: 1203-1215.

90. Eleftheriou D, Levin M, Shingadia D, Tulloh R, Klein NJ, et al. Management of Kawasaki disease. Arch Dis Child. 2014; 99: 74-83.

91. Freeman AF, Shulman ST. Refractory Kawasaki disease. Pediatr Infect Dis J. 2004; 23: 463-464.

92. Stenbøg EV, Windelborg B, Hørlyck A, Herlin T. The effect of TNFalpha blockade in complicated, refractory Kawasaki disease. Scand J Rheumatol. 2006; 35: 318-321.

93. Rodríguez-González M, Matamala-Morillo MA, Segado-Arenas A . Infliximab as rescue therapy in refractory Kawasaki disease. Ann Pediatr Cardiol. 2014; 7: 74-75.

94. Weiss JE, Eberhard BA, Chowdhury D, Gottlieb BS. Infliximab as a novel therapy for refractory Kawasaki disease. J Rheumatol. 2004; 31: 808-810.

95. Son MB, Gauvreau K, Burns JC, Corinaldesi E, Tremoulet AH, et al. Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: a retrospective study. J Pediatr. 2011; 158: 644-649.

96. Dominguez SR, Anderson MS. Advances in the treatment of Kawasaki disease. Curr Opin Pediatr. 2013; 25: 103-109.

97. Sandi C Lin, Wan-Lin Tseng, Mindy Ming-Huey Guo and Ho-Chang Kuo, Etanercept as Rescue Therapy for Refractory Kawasaki Disease. Austin J Pediatr. 2014;1(2): 1010.

98. Bartolucci P, Ramanoelina J, Cohen P, Mahr A, Godmer P, et al. "Efficacy of the anti-TNF-a antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients". Rheumatology. 2002; 41: 1126-1132.

99. Lamprecht P, Voswinkel J, Lilienthal T, Nolle B, Heller M, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. Rheumatology (Oxford). 2002; 41: 1303-1307.

100. Booth AD, Jefferson HJ, Ayliffe W, Andrews PA, Jayne DR. Safety and efficacy of TNF-alpha blockade in relapsing vasculitis. Ann Rheum Dis. 2002; 61: 559.

101. Morgan MD, Drayson MT, Savage CO, Harper L. Addition of infliximab to standard therapy for ANCA-associated vasculitis. Nephron Clin Pract. 2011; 117: c89-97.

102. De Menthon M, Cohen P, Pagnoux C, Buchler M, Sibilia J, et al. "Infliximab or rituximab for refractory Wegener's granulomatosis: long-term follow-up. A prospective randomised multicentre study on 17 patients". Clinical and Experimental Rheumatology-Incl Supplements. 2011; 29: S63-71.

103. Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, et al. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. Arthritis Rheum. 2001; 44: 1149-1154.

104. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med. 2005; 352: 351-361.

105. Laurino S, Chaudhry A, Booth A, Conte G, Jayne D. "Prospective study of TNFa blockade with adalimumab in ANCA-associated systemic vasculitis with renal involvement". Nephrology Dialysis Transplantation. 2010; 25: 3307-3314.

106. Kussmaul A MR. Ueber eine bisher nicht beschriebene eigenthümliche arterienerkrankung (periarteritis nodosa), die mit morbus brightii und rapid fortschreitender allgemeiner muskellähmung einhergeht. Deutsche Arch Klin Med. 1866; 1: 484-518.

107. Dillon MJ, Eleftheriou D, Brogan PA. Medium-size-vessel vasculitis. Pediatr Nephrol. 2010; 25: 1641-1652.

108. Watts RA, Scott DG. Epidemiology of the vasculitides. Semin Respir Crit Care Med. 2004; 25: 455-464.

109. Ettlinger RE, Nelson AM, Burke EC, Lie JT. Polyarteritis nodosa in childhood a clinical pathologic study. Arthritis Rheum. 1979; 22: 820-825.

110. Grau GE, Roux-Lombard P, Gysler C, Lambert C, Lambert PH, et al. Serum cytokine changes in systemic vasculitis. Immunology. 1989; 68: 196-198.

111. Ng WF, Chow LT, Lam PW. Localized polyarteritis nodosa of breast--report of two cases and a review of the literature. Histopathology. 1993; 23: 535-539.

112. Pagnoux C, Seror R, Henegar C, Mahr A, Cohen P, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. Arthritis Rheum. 2010; 62: 616-626.

113. Provenzale JM, Allen NB. Neuroradiologic findings in polyarteritis nodosa. AJNR Am J Neuroradiol. 1996; 17: 1119-1126.

114. Capuozzo M, Ottaiano A, Nava E, Cascone S, Fico R, et al. Etanercept induces remission of polyarteritis nodosa: a case report. Front Pharmacol. 2014; 5: 122.

115. Falk RJ, Nachman PH, Hogan SL, Jennette JC . ANCA glomerulonephritis and vasculitis: a Chapel Hill perspective. Semin Nephrol. 2000; 20: 233-243.

116. Guillevin L. [How to treat systemic necrotizing vasculitides?]. Presse Med. 2012; 41: 1024-1030.

117. Fauci AS, Haynes BF, Katz P, Wolff SM. "Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years". Annals of internal medicine. 1983; 98: 76-85.

118. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008; 359: 2790-2803.

119. Stassen PM, Tervaert JW, Stegeman CA. "Induction of remission in active anti-neutrophil cytoplasmic antibody-associated vasculitis with mycophenolate mofetil in patients who cannot be treated with cyclophosphamide". Annals of the rheumatic diseases. 2007; 66: 798-802.

120. Guillevin L. Rituximab for ANCA-associated vasculitides. Clin Exp Rheumatol. 2014; 32: S118-121.

121. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med. 2013; 369: 417-427.

122. Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, et al. "Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody–associated vasculitis". Arthritis & Rheumatism. 2012; 64: 3760-3769.

123. Charles P, Néel A, Tieulié N, Hot A, Pugnet G, et al. "Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients". Rheumatology. 2014; 53: 532-539.

124. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford). 2014; 53: 2306-2309.