Clinical Rheumatology (2019) 38:2825–2833
https://doi.org/10.1007/s10067-019-04474-9

CASE BASED REVIEW

Infliximab for the treatment of refractory polyarteritis nodosa

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Received: 30 December 2018 / Revised: 29 January 2019 / Accepted: 7 February 2019 / Published online: 10 April 2019

Abstract

Polyarteritis nodosa (PAN) is a necrotizing vasculitis predominantly affecting medium and small size arteries. Cyclophosphamide, a drug with narrow therapeutic range and poor safety profile, constitutes the treatment of choice for PAN vasculitis with major organ involvement. To describe our clinical experience in treating refractory PAN with infliximab (a TNF inhibitor), a drug with good tolerability and better safety profile than cyclophosphamide. Twenty-six PAN patients were admitted to our rheumatology unit between 2006 and 2017, of whom nine patients, with severe and refractory disease, were treated with infliximab after failure of standard treatment. We describe herein the patients' characteristics, clinical manifestations, severity and response to infliximab treatment and review the current literature. Complete remission was defined as the absence of features of active disease and withdrawal of prednisone therapy. Significant improvement was defined as clinical improvement and prednisone dose reduction of at least 50% or a 50% reduction in immune modulatory medications other than prednisone. After 4 months of treatment, 8/9 (89%) patients achieved significant improvement, with two of them achieving complete remission. We suggest that anti-TNF agents, and in particular infliximab, are relatively safe and efficacious treatment options in refractory PAN. A randomized controlled trial should be done in order to objectively evaluate infliximab in PAN.

Keywords Infliximab · Polyarteritis nodosa

Introduction

Polyarteritis nodosa (PAN) is a necrotizing vasculitis predominantly affecting medium and small size arteries [1].

The skin and peripheral nervous system are the most frequently involved target organs followed by the gastrointestinal tract and the kidneys—involvement of which indicates a poor prognosis. Any organ may be involved, yet the lungs are usually spared. Consequently, PAN is characterized by a wide range of clinical manifestations [2].

Diagnosis of PAN is based on the clinical manifestations and histopathological evidence of necrotizing inflammation in small or medium artery walls. The acute phase of arterial wall inflammation is characterized by fibrinoid necrosis of the media. Angiographic evidence of microaneurysms is useful in patients with a clinical picture suggestive for PAN where biopsy is not feasible [3].

The 1996 Five-Factor Score (FFS), devised to assess necrotizing vasculitides, was previously used to evaluate the severity of the disease at presentation and helped the physician to determine the need for immunosuppression.

The revised 2009 FFS is composed of the following criteria: age > 65 years, cardiac insufficiency, renal insufficiency, and gastrointestinal involvement. The fifth point, absence of ENT manifestations is scored + 1 point, regards only granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [4]. This revised Score has not been validated as a guide for therapy in PAN (as opposed to the old FFS), but serves as a prognostic score.

Glucocorticoids and cyclophosphamide are the cornerstones of PAN therapy.

Glucocorticoids are used in patients without major organ involvement. Conversely, in the presence of critical ischemia in one of the major target organs, induction with cyclophosphamide is added.

Classically HBV-related PAN (HBV-PAN) was prevalent (30% of the cases) and was described as a monophasic

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disease, which usually resolves after induction treatment [5]. However, widespread use of the hepatitis B vaccine has significantly decreased the incidence of HBV-PAN, which is now estimated to account for less than 8% of all PAN cases [6]. Non-HBV-related PAN is becoming more prevalent and is characterized with a chronic course that demands long-term treatment [7]. Severe cases with major organ involvement as gastrointestinal tract, kidneys, and heart or brain are challenging, yet even patients without so-called severe vasculitis, yet suffering from necrotizing/scarring deep skin vasculitis, frequently accompanied by neuropathy, suffer great pain and their quality of life is dramatically impaired. Cyclophosphamide, the mainstay therapy is a drug with some severe adverse effects, among which are myelosuppression, bladder toxicity that may manifest in hemorrhagic cystitis, cardiotoxicity, and pulmonary toxicity (that may cause pulmonary fibrosis). Moreover, cyclophosphamide is teratogenic and may cause infertility, a fact that precludes its use in many of the affected patients at a child-bearing age [8]. Last, but not least, is the oncogenic potential of cyclophosphamide that includes transitional cell carcinoma of bladder, myelodysplasia, acute leukemias, lymphomas, and skin cancer [9], which makes its long-term use unacceptable. Hence, although effective, cyclophospahmide is a drug with many untoward effects, to which alternative treatments in case of failure or intolerability are scarce and the scientific evidence is lacking. The young age of many patients and chronicity of disease requires an alternative treatment.

Several biological treatments for PAN, including anti-tumor necrosis factor (TNF) agents, tocilizumab, tofacitinib, and rituximab, have been described in the literature with varying results [10–14].

We describe herein our experience in treating refractory PAN with infliximab (a TNF inhibitor), a drug with better safety profile than cyclophosphamide, good tolerability and safety with regard to pregnancy in fertile women.

Our experience with TNF inhibitors for PAN treatment

In this review, we describe our therapeutic experience with infliximab in adult patients with severe PAN who failed standard treatment.

Patients characteristics

Reviewing all vasculitis patients who were admitted to our rheumatology unit between 2006 and 2017, we identified 26 patients with the diagnosis of PAN, of whom 9 were treated with infliximab after failure of standard treatment.

Table 1 summarizes the characteristics of these patients.

Of the 9 patients treated with infliximab, 7 were males and 2 were females. Their mean age was 36 years (range 14–67 years) at the time of diagnosis.

None of the patients was a HBV carrier. All patients met the 1990 American College of Rheumatology (ACR) classification criteria and the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides for PAN [1, 15]. Serologic tests and immunofluorescence of all patients were negative to anti-neutrophil cytoplasmatic antibody, anti-proteinase 3, anti-myeloperoxidase antibody, and antinuclear antibody.

The diagnosis was confirmed histologically by skin biopsy showing arteries with vasculitis and fibrinoid necrosis in 8 patients (patient nos. 1–5, 7–9) and by demonstration of aneurysms on CT or formal angiography in 4 patient (patient nos. 4, 6, 7, 9) (Figs. 1 and 2).

Two patients (nos. 5 and 7), of Georgian Jewish ancestry who had skin lesions and CNS involvement, were found to carry the adenosine deaminase 2 (ADA-2) mutation.

This cohort's clinical manifestations ranged widely (Table 1), yet all patients presented a severe, chronic disease, refractory to standard treatment, with a mean revised FFS on presentation of 0.67 (range 0–2).

Eight patients presented with severe necrotizing cutaneous vasculitis (patient nos. 1–5, 7–9); 6 patients had peripheral arthritis (patient nos. 1–5, 8); 2 patients had CNS involvement (nos. 5, 7); 2 patients suffered from incapacitating myalgia (nos.1, 2), and one patient suffered renal hemorrhage (patient no. 4).

All patients were treated with varying doses of prednisone. The patients were treated initially with conventional therapy, 7 with methotrexate (MTX) (nos. 1–4, 6, 8, 9) and 5 with azathioprine (AZA) (nos. 1, 3, 5, 8, 9) and were switched to cyclophosphamide or infliximab.

Seven patients failed treatment with IV cyclophosphamide 500 mg every other week (patients nos. 2–5, 7, 8, 9) and 2 patients (no. 1, 6) were treated with infliximab right after failure of conventional therapy with methotrexate or azathioprine.

Infliximab treatment 5 mg/kg was initiated after a mean disease duration of 7.5 years and was administered at 0, 2, and 6 weeks, then every 6 weeks.

Response to infliximab

Complete remission was defined as the absence of features of active disease and withdrawal of prednisone therapy.

Significant improvement was defined as clinical improvement and prednisone dose reduction of at least 50% or a 50% reduction in the total number of medications other than prednisone.

Table 1 Patient characteristics and response to Infliximab treatment

Pt no.	M/F	Age*	PAN diagnosis[#]	Disease duration until INF[&]	Main clinical manifestation at presentation	FFS	Treatments prior to infliximab therapy[&]	Treatment at time of infliximab initiation PDN other	Treatment 4 months after infliximab initiation PDN other	Clinical outcome with infliximab
1	M	18	Skin biopsy	9 years	Cutaneous, myalgia arthritis	0	MTX, IMURAN, CsA, prednisone	5 mg Imuran 100 mg, CsA 100 mg, MTX 15 mg/w	5 mg MTX 15 mg	Arthritis and rash improved. No pain
2	M	41	Skin biopsy	19 years	Cutaneous (purpura, ulcers) myalgia arthritis	0	CYC, MTX, potassium iodide, PDN, iloprost, IVIG	10 mg Iloprost 50 mcg, MTX 15 mg/w	0 MTX 7.5 mg	Ulcers were healed. No purpura. No arthritis. No pain
3	M	14	Skin biopsy	10 years.	Cutaneous, arthritis, orchitis	0	AZA, MTX, IVIG, CYC, CsA, PDN	30 mg IVIG, MTX 15 mg/w	20 mg MTX 15 mg	Very good clinical response in all indices
4	M	28	Skin biopsy, renal aneurysms, SMA aneurysms on CT	6 months	Cutaneous, arthritis, renal aneurysm, SMA aneurysm, pulmonary effusion, renal hemorrhage, proteinuria, HTN	2	MTX, PDN, CYC, IVIG, ETN	40 mg Plasmapheresis, MTX 15 mg/w	15 mg MTX 12.5 mg	Very good clinical response in all indices
5	M	33	Skin biopsy, ADA mutation	2 years	Cutaneous, CNS, arthritis, HTN	0	AZA, PDN, CYC, potassium iodide, CsA	10 mg CsA 100 mg, Po CYC 100 mg	10 mg CsA 100	Ulcers were healed. No arthritis
6	F	67	Renal + hepatic aneurysms	8 yeas	GI	2	MTX, PDN	15 mg MTX 7.5 mg/w	7.5 mg MTX 7.5 mg	Very good clinical response.
7	F	16	Angiography, brain aneurysms, skin biopsy ADA mutation	4 years	Cutaneous,, digital ulcers, cerebral vasculitis, cerebral aneurysms, CVA, seizures	0	PDN, PLQ, CYC, aspirin, warfarin, iloprost	20 mg PLQ 400 mg, CYC 500 mg/14 days, aspirin, warfarin	10 mg MTX 15 mg	Very good clinical response, inflammatory markers decreased. Seizures stopped improvement in ulcers
8	M	49	Skin biopsy	1.5 years	Cutaneous, testicular pain. Polyneuropathy, arthritis, HTN	0	PDN, MTX, AZA, CYC	10 mg –	5 mg –	Very good clinical response in all indices except polyneuropathy
9	M	57	Skin biopsy + abdominal aneurysms on angiography	8 years	Cutaneous, neuropathy, elevated liver enzymes, Renal GI.	2	PDN, MTX, AZA, CYC	15 mg MTX 15 mg/w, AZA 100 mg	0 MTX 15 mg AZA 100 mg	Very good clinical response in all indices

M/F male/female. *FFS* 2009 revised Five-Factor Score, *SMA* superior mesenteric artery, *PDN* prednisone, *INF* infliximab, *MTX* methotrexate, *CYC* cyclophosphamide, *IvIg* intravenous immunoglobulins, *ETN* etanercept, *AZA* azathioprine, *CsA* cyclosporine A

*Age (years, when PAN was diagnosed) FFS – 2009 Revised Five Factor Score SMA – Superior mesenteric artery

[#] All patients met the 1990 American College of Rheumatology classification criteria (ACR) and the 2012 revised international Chapel Hill Consensus Conference Nomenclature of vasculitis for PAN [1, 15]

[&] The first time INF was administered

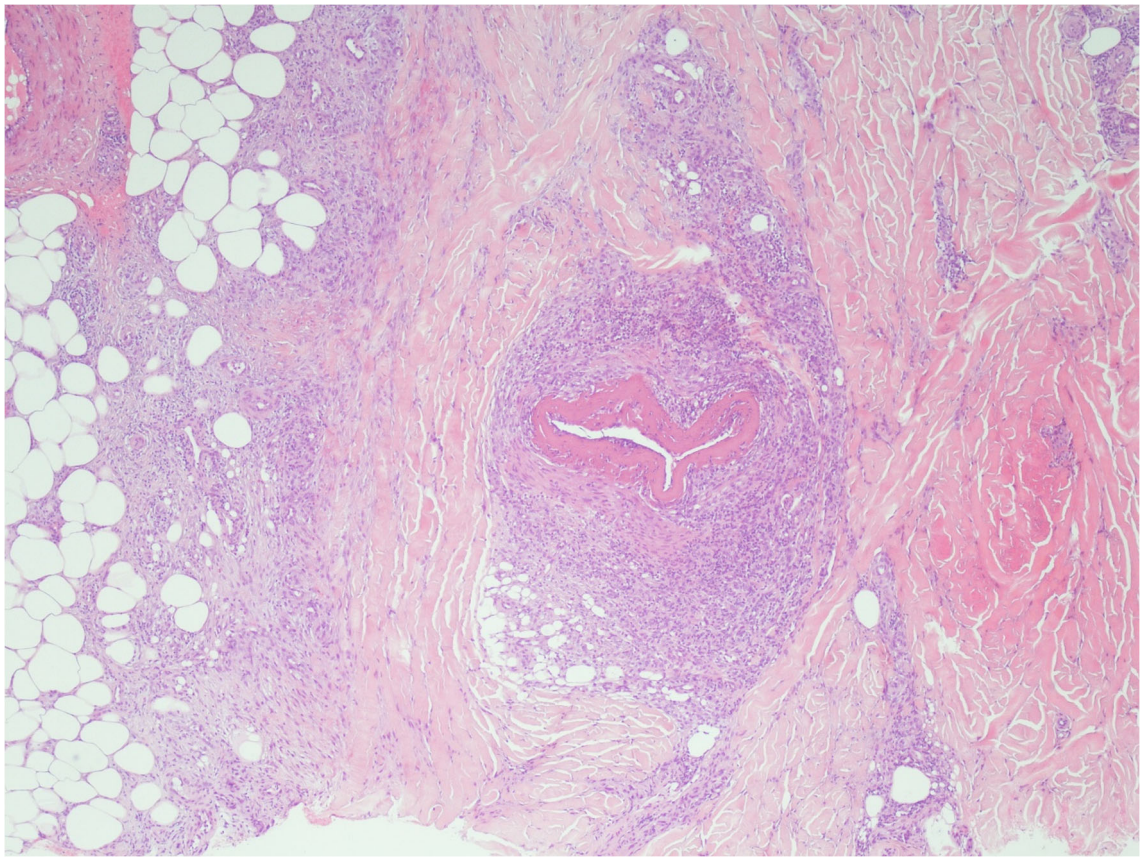

Fig. 1 A Skin biopsy of patient no. 8 showing a small artery vessel with fibrinoid necrosis and neutrophilic infiltration

In rheumatoid arthritis, response to infliximab therapy may be seen rapidly, with more than 50% of patients showing some improvement after 2 weeks of treatment initiation and approximately 90%, of those responding, after 6 weeks of treatment [16].

We evaluated the response to infliximab after 4 months, a duration that may be considered sufficient to evaluate the efficacy of infliximab.

After 4 months of treatment, 8/9 (89%) patients achieved significant improvement, with two of them achieving complete remission.

The mean prednisone dose was 17.2 mg before infliximab (range 5–40 mg) and decreased to 8.1 mg (0–20 mg) 4 months after infliximab was initially administered. The mean total number immunosuppressive drugs for PAN that were prescribed in addition to prednisone was 2 before initiation of infliximab and decreased to 1, on average, following infliximab treatment.

All these patients suffered from severe and recurrent disease, as opposed to the classic monophasic disease that was previously described in HBV-related PAN. In line with our findings, recent studies have shown a relapse rate higher than previously reported in this disease [17]. We assume it is a consequence of the decline in HBV infection (possibly following vaccination) as a cause of classic monophasic PAN.

Most of our patients presented with severe cutaneous necrotizing vasculitis. Although skin manifestation is not included in the FFS, it results in pain and a major impact on quality of life. Hence, despite severe and refractory disease, the FFS was lower than expected.

Safety One patient (no. 8) developed an allergic serum sickness like reaction 5 months after starting infliximab treatment, and the treatment was switched to adalimumab.

Another patient (no. 6) developed neurologic transient ischemic attack like symptoms, 1 year following Infliximab treatment, and the treatment was halted.

None of our patients developed serious infections or tuberculosis while treated with infliximab.

Literature review

A PubMed search for the terms “anti-tumor necrosis factor,”, “infliximab,” and “polyarteritis nodosa” yielded 19 relevant English reports, excluding duplicate reports from the same center.

Table 2 [10, 14, 18–28] summarizes the data of a total of 32 PAN patients that were reportedly treated with anti-TNF agents between 2003 and 2017, of whom 25 were children

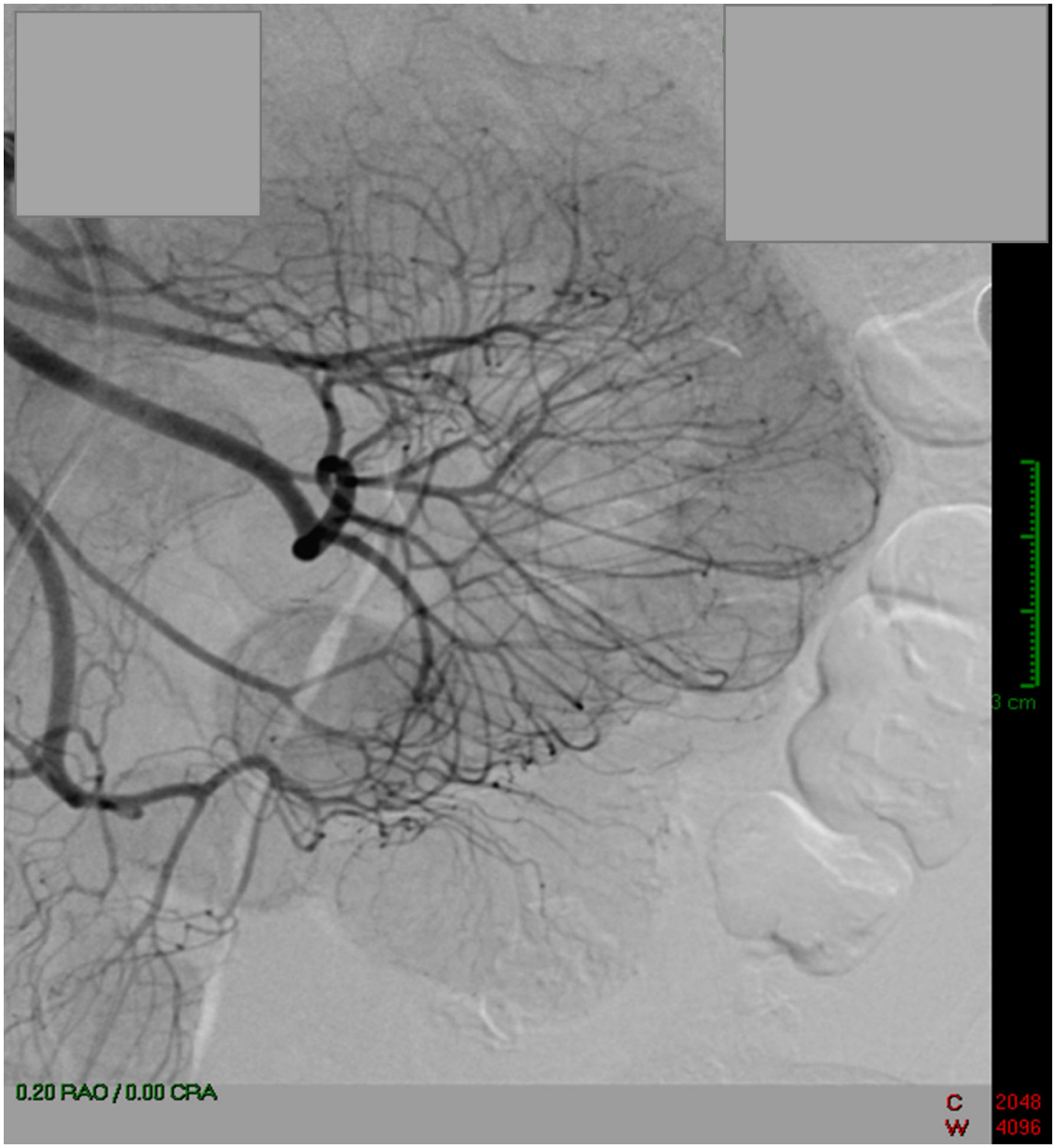

Fig. 2 Patient no. 9 angiography demonstrating small microaneurysms in the right renal artery

and only 7 cases were adults; 6 of those 7 adult patients were treated with Infliximab.

Experience with infliximab treatment for PAN in pediatric patients

Among the children reported, the manifestations of the disease varied, ranging from disease limited to the skin—manifesting as severe ulcers and livedo reticularis—to severe systemic multi-organ involvement, including recurrent stroke or cerebral hemorrhage at a young age.

A subgroup of pediatric patients diagnosed as PAN, carried an autosomal recessive mutation in the cat eye syndrome chromosome region, candidate 1 (CECR1) gene, which encodes adenosine deaminase 2 (ADA-2). In this population, currently termed DADA2 (deficiency of ADA2), treatment with TNF-α antibodies in patients with insufficient response to conventional therapy was found to be particularly effective [26, 29].

Previous experience with infliximab treatment for PAN in adult patients

In all, 6 adults with PAN, 4 males and 2 females, successfully treated with infliximab, have been previously reported in the literature (Table 2). The mean age of these patients was

Table 2 Case reports of patients with refractory PAN—successfully treated with anti-TNF treatment

Article (references [10, 14, 18–28])	No. of pts.	Age	Clinical manifestation	Revised FFS	TRX	Anti-TNF	Outcome
Biologic therapy in primary systemic vasculitis of the young [14]	11	2.4–16	Systemic + cutaneous including CNS with neurologic insult.	0–1	MTX, colchicine, CsA, IVIG, AZA Tha PE, MMF	INF, ETN, ADA	Significant decline in the median daily prednisone dose. Significant reduction in the BVAS score
Successful treatment of childhood cutaneous polyarteritis nodosa with infliximab [18]	1	14	Cutaneous	0	PDN	INF	Remission
Etanercept induces remission of PAN [19]	1	10	Polyarthritis, myalgias, LR, brain lesions, polyneuropathy	0	PDN—2 years CYC Ivig Tha	ETN	Remission
Remission induced by infliximab in a childhood polyarteritis nodosa refractory to conventional immunosuppression and rituximab [20]	1	3	Fever, arthritis, and subcutaneous nodular, painful, purpuric lesions in his extremities	0	PDN—asymptomatic for 10 years. Exacerbation: PDN MTX CYC RTX	INF	Remission
ADA2 deficiency: case report of a new phenotype and novel mutation in two sisters [21]	2	3.5 1	Fever, cutaneous vasculitis, myalgia, CNS anemia lymphopenia	0 0	GCS CsA, AZA, CYC	ETN Anti TNF	Remission
A case of refractory cutaneous polyarteritis nodosa in a patient with hepatitis B carrier status successfully treated with tumor necrosis factor alpha blockade [22]	1	60	Cutaneous lesions (purpura, livedo reticularis, subcutaneous nodules), arthritis, neuropathy arthralgias, myalgias,	0	PDN, MTX, CsA, TAC, AZA, Colchicine, CYC.	ETN	Remission for 8 months. No data available afterwards
Infliximab in a child with therapy-resistant systemic vasculitis [25]	1	10	Cutaneous MSK GI Pericardial effusion	2	AZA, PLQ GCS	INF	Remission
Cranial nerve involvement with juvenile polyarteritis nodosa: clinical manifestations and treatment [27]	1	20 months	Fever, mouth sores, livedo reticularis, subcutaneous nodules cranial nerve III palsy, intracranial hemorrhage.	0	GCS MTX CYC MMF	ETN INF	Remission
Cont. Adults patients that were treated with infliximab							
The Successful Treatment of Refractory Polyarteritis Nodosa Using Infliximab [10]	1	64	Hypertension, ankles arthritis, testicular lesion	0	PRD MTX Po CYC TAC RTX	INF	Improvement after 4 months. No data available afterwards
A new treatment for polyarteritis nodosa [23].	1	69	Fever, abdominal pain, purpuric rash, renal failure and hemorrhage, disseminated intravascular coagulation (DIC), hypertension, renal artery aneurysm	1	PDN, AZA, CYC,	INF	Improvement. Marked improvement in the renal vasculature.
Refractory polyarteritis nodosa successfully treated with infliximab [24]	1	33	Abdominal pain, chronic diarrhea livedo reticulars, arthritis hydronephrosis mononeuritis multiplex	1	PDN, CYC, IVIG,MTX, AZA	INF	Dramatic improvement. Healing of the gangrenous ulcers on the legs. Mononeuritis multiplex improved.
Deficiency of adenosine deaminase type [26]	15 (9 patients were treated with anti TNF, 2 adults were treated with INF)	5–42	5, asymptomatic; 10, livedo recamosa, neurologic manifestation, immunodeficiency	0	PRD colchicine CYC AZA MMF RTX IVIG PRD IV CYC TCZ	9/10 Anti TNF. 4(2 adults) IFX 5 ADA	No information available for these 2 patients, but prednisone dose was decreased
Large leg ulcers due to autoimmune diseases [28]	1	20	Livedo reticularis, Large leg ulcers, fever, ocular palsy, acute intestinal ischemia and perforation, polyneuropathy	1	GCS CYC IvIg	INF	Improvement in neurologic and general condition; ulcers were healed.

PDN prednisone, *AB* antibiotics, *INF* infliximab, *GCS* glucocorticosteroids, *MTX* methotrexate, *CYC* cyclophosphamide, *IvIg* intravenous immunoglobulins, *ETN* etanercept, *RTX* rituximab, *AZA* azathioprine, *ADA* adalimumab, *CsA* cyclosporine A, *MMF* mycophenolate mofetil, *Tha* thalidomide, *PLQ* plaquenil, *TCZ* tocilizumab, *SSZ* sulfasalazine, *PE* Plasma exchange, *TAC* tacrolimus, MSK Musculoskeletal, *BVAS* Vasculitis Activity

39 years (range 20–69 years). None of these patients was an HBV carrier. Two patients were found to carry the ADA-2 mutation [29].

The diagnosis was confirmed by skin biopsy in 3 patients [10, 24, 28] and by identification of aneurysms on CT or formal angiography in 3 patients [23, 24, 26]. The average revised FFS on presentation was 0.5 (range 0–1). All patients presented with cutaneous vasculitis. The two patients who carried the ADA-2 mutation had intracranial hemorrhage [26]. One patient suffered renal hemorrhage [23], and one had intestinal ischemia [28].

Prior to infliximab therapy, all these patients had been treated with varying doses of prednisone and cyclophosphamide. Only two patients were treated with MTX [11, 24] and 3 with AZA [23, 24, 26]. One patient [10] was treated with infliximab after failure of rituximab.

All patients improved clinically and prednisone dose was decreased by more than 50% following infliximab.

Discussion

We have presented herein 9 patients with severe and persistent PAN, refractory to the standard treatment, who were treated with infliximab successfully, with good clinical and laboratory response.

The first reports of the use of infliximab in vasculitis were described by Gary Hoffman et al. in patients with Takayasu arteritis [30]. The efficacy of infliximab in granulomatous diseases may explain partly its effect in Takayasu, a granulomatous vasculitis. PAN has a different pathophysiology, yet several lines of evidence may serve to explain the efficacy of infliximab in vasculitis in general and PAN in particular.

Infliximab is a monoclonal chimeric antibody (mouse/human) that acts against TNF-α.

TNF-α is proinflammatory cytokine, produced by macrophages and dendritic cells in two forms: a transmembranal form that is then split by TNF-α-converting enzyme (TACE) into the soluble form. These two forms bind to two ubiquitous cell surface receptors (TNFR1 and TNFR2) on target cells to initiate transcription of genes. This action is mediated through the activation of nuclear factor kappa B (NFκB) and mitogen-activated protein (MAP) in addition to protein gene transcription.

Among its many activities, TNF-α mediates the binding of leukocytes to endothelium through adhesion molecules such as E-selectin, intercellular adhesion molecule 1 (ICAM-1), and vascular adhesion molecule 1 (VCAM-1). This binding promotes chemotaxis and recruitment of leukocytes into tissue.

TNF-α also mediates the production of other proinflammatory cytokines, the activation of other immune cells such as B cells, T cells, macrophages, while having an inhibitory effect on regulatory T cells.

Additionally, TNF-α participates in mediating cell death through neutrophil activation or directly through apoptosis. [31, 32].

A number of previous studies have attempted to examine whether there is a correlation between TNF-α expression and systemic vasculitis.

Grau GE et al. [33] examined cytokine levels including TNF-α in the serum of patients with vasculitis, including PAN. They found that TNF-α levels were moderately elevated, whereas IFN-a and IL-2 levels were markedly increased. The levels of those cytokines decreased dramatically after immunosuppressive therapy, mainly in PAN patients.

Their conclusion was that a particular pattern of cytokine change is associated with vasculitis and that cytokines might be involved in the pathogenesis of necrotizing vasculitis.

Deguchi Y et al. [34] examined the TNF-α gene expression in peripheral blood mononuclear cells in patients with vasculitis (PAN and GPA), in addition to transcriptional level of TNF-a gene in these cells. They found increased amount of TNF-α mRNA in peripheral blood mononuclear cells from PAN and GPA patients compared with healthy subjects, as well as elevated serum TNF levels, and concluded that TNF-α has an important role of in the pathophysiology of systemic vasculitis.

Hence, several lines of evidence support a possible role for anti-TNF treatment in systemic vasculitis and specifically in PAN.

Study limitations Of notice, is the fact that two of our patients carry the mutation of ADA-2 and represent a sub population of PAN, in which a good response to infliximab has been described before and thus may have positively biased our impression.

These results should be interpreted cautiously as this cohort represents a retrospective analysis of preselected population of patients that have failed conventional therapy.

Conclusion

PAN is a severe, progressive disease with multi-organ involvement that affects young patients frequently with long-term course and many relapses that endanger and impair quality of life. The treatment of choice for severe disease is cyclophosphamide, a teratogenic drug with many side effects and oncogenic potential that precludes its long-term use.

We have presented herein our experience with infliximab in severe refractory PAN and reviewed the current literature. We suggest anti TNF agents, and in particular infliximab, are relatively safe and efficacious treatment options in refractory PAN, that can be used safely long term. A publication bias

of positive reports should be considered, and a randomized controlled trial should be done in order to objectively evaluate infliximab in PAN.

Compliance with ethical standards

Disclosures None.

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