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Biologic therapy in primary systemic vasculitis of the young

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Objectives. To describe the biologic treatment regimens and report the efficacy and safety of biologic therapies in a multicentre series of children with primary systemic vasculitis (PSV).

Methods. This was a retrospective descriptive case series of children with PSV treated with biologic therapy between February 2002 and November 2007. Primary retrospective outcome assessment measures were: daily corticosteroid dose; Birmingham Vasculitis Activity Score (BVAS); and adverse events (including infection rate).

Results. Twenty-five patients median age 8.8 (range 2.4–16) years; 11 male with active PSV ($n=6$ with anti-neutrophil cytoplasmic antibody associated vasculitides, $n=11$ with polyarteritis nodosa, $n=7$ with unclassified vasculitis and $n=1$ with Behçet's disease) were treated with biologic agents including infliximab ($n=7$), rituximab ($n=6$), etanercept ($n=4$), adalimumab ($n=1$) or multiple biologics sequentially ($n=7$). Overall, there was a significant reduction in BVAS from a median of 8.5 (range 5–32) at start of therapy to 4 (range 0–19) at median 32 months follow-up ($P=0.003$) accompanied by significant reduction in median daily prednisolone requirement from 1 (range 0.2–2) to 0.25 (range 0–1) mg/kg/day, $P=0.000$. For those receiving multiple biologic agents sequentially, a similar clinical improvement was observed with corticosteroid sparing. Infections occurred in 24%, the most severe in those receiving infliximab.

Conclusion. Our data provide retrospective evidence of efficacy of these agents, and highlight the associated infectious complications. Further multicentre standardization of treatment protocols and data collection to inform clinical trials of biologic therapy in systemic vasculitis of the young is required.

Key words: Primary systemic vasculitis, Children, Biologic therapies, Birmingham Vasculitis Activity Score, Infection rate.

Introduction

Primary systemic vasculitis (PSV) of the young is characterized by the presence of inflammation in the walls of blood vessels, with resultant tissue ischaemia and necrosis [1]. Primary vasculitic syndromes include, amongst others, HSP, Kawasaki disease (KD), PAN, Takayasu disease (TD) and the ANCA-associated vasculitides (AAV), comprising WG, microscopic polyangiitis (MPA), renal limited vasculitis and Churg-Strauss syndrome [1]. Although rare in the young, PSV is still associated with significant morbidity and mortality [2, 3].

The current first line treatment for severe PSV (excluding KD and HSP) includes combined therapy with corticosteroids and cyclophosphamide, sometimes with plasma exchange for patients with severe and/or multi-system involvement particularly for AAV or PAN [4–6]. However, treatment-associated toxicity, particularly sepsis, infertility and increased cancer risk, remains as major concern particularly in the young [7, 8]. Overall, treatment-associated adverse events occur in 25% of the patients during the first year of therapy [9]. Furthermore, although primary treatment failure is uncommon, many patients experience disease relapse as treatment is weaned [10–12].

Novel biologic therapies targeted against specific components of the immune system, including (amongst others) blockade of TNF-α, IL-1, or B lymphocytes, have already revolutionized therapeutic approaches to other autoimmune diseases such as juvenile idiopathic arthritis, and are increasingly used (albeit with a less firm evidence base) in SLE [13, 14]. Data describing efficacy and/or adverse events relating to the use of biologic therapy for PSV in children are limited, however, and at present based on case reports describing small numbers of patients [15–17].

The aim of the present study therefore was to describe our 5-year retrospective experience of using biologic therapy in PSV of the young with reference to clinical indication, choice of biologic regimen, efficacy and safety.

Patients and methods

This was a retrospective descriptive case series of children with PSV treated with biologic therapy. Patients were identified through a review of the Great Ormond Street Hospital for Children (GOSH) vasculitis database from its inception in February 2002 through November 2007, with subsequent retrospective case notes review. This project was registered with and given ethical approval by the research and development department of Great Ormond Street Hospital and Institute of Child Health as a retrospective case series data collection. The 21 patients from GOSH were recruited from a designated vasculitis clinical service with standardized protocols of investigation, classification of disease and treatment thus facilitating retrospective data collection. Additionally, UK and European collaborators of the Paediatric Rheumatology European Society (PRES) vasculitis working party were contacted via email for further identification of patients. Inclusion in the study required the following: age at the time of biologic treatment of <16 years old, a diagnosis of PSV (clinical diagnosis with radiological and/or histopathological confirmation) and treatment with one or more biologic therapies (anti-TNF-α, rituximab, anakinra or other).

Biologic therapy used

Biologic agents used included infliximab (human chimeric anti-TNF-α monoclonal antibody), etanercept (a fusion protein of the p75 TNF-α receptor and IgG1), adalimumab (a fully humanized IgG1 anti-TNF-α monoclonal antibody), rituximab

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(anti-CD20 chimeric mouse/human monoclonal antibody) and anakinra (recombinant IL-1 receptor antagonist).

Classification criteria for vasculitic syndromes

Classification of vasculitis was according to the definitions described in the Chapel Hill Consensus Conference (CHCC) proposal for a standard nomenclature of systemic vasculitides [18] and the ACR criteria [19] (Table 1). In addition, although the new European League against Rheumatism (EULAR)/Pediatric Rheumatology European Society (PRES) consensus classification criteria for vasculitis of the young are currently undergoing validation, these criteria were applied as an additional classification tool [20]. The term unclassified vasculitis (UCV) was used to describe patients with histological and/or angiographic evidence of vasculitis, but who did not fulfil classification criteria for any of the above classification systems.

Duration of follow-up and treatment responses post-biologic treatment

A minimum follow-up period of 3 months following administration of biologic therapy was required for inclusion. Treatment responses were assessed by changes in Birmingham Vasculitis Activity Scores (BVAS) (see below), CRP, ESR and the daily dose of prednisolone administered. A modified version of the BVAS incorporating age-specific laboratory reference ranges was used to retrospectively assess vasculitic disease activity [21]. Active vasculitis was thus defined as a BVAS >0 with BVAS items newly appearing or worse in the preceding 4 weeks and attributable to vasculitis, with the exclusion of other causes such as infection. Disease remission was defined as BVAS 0/63. Evaluation was performed at the time of initiation of treatment and at the time of latest follow-up. For the patients who received more than one biologic agent an additional assessment was performed at the time of change of treatment.

Statistical analysis

Patient demographics were summarized as median and range unless otherwise stated. Changes in paired continuous variables in response to biologic therapy were compared using the Wilcoxon signed ranks test. P-values < 0.05 were considered significant. Statistical analysis was performed using SPSS version 15.

Results

Patient characteristics and vasculitis classification

A total number of 25 patients who fulfilled the inclusion criteria were identified. Twenty-one of these children were patients at Great Ormond Street Hospital; two patients were from the Alder Hey Children's NHS Foundation Trust, Liverpool, UK; and two patients were from the Department of Paediatrics, Hacettepe University, Medical Faculty, Ankara, Turkey. The median age of the patients at diagnosis of vasculitis was 7 (range 0.6–15.3) years, while the median age at the time of treatment with biologic therapy was 8.8 (range 2.4–16) years. Table 1 summarizes the clinical characteristics of these patients.

The vasculitis type classified using the CHCC was: PAN ($n=11$); WG ($n=5$); MPA ($n=1$); and unclassified vasculitis ($n=8$) (Table 1). Of note, there was great agreement in the classification of vasculitides between the three different classification systems used. The diagnosis of vasculitis was based on arteriography alone in 5/25 patients; histopathological evidence of vasculitis in 10/25; and both histology and arteriography in 6/25 patients. In the remaining four patients, the diagnosis of vasculitis was clinical (Patients 3, 23, 24 and 25).

Conventional treatment received prior to biologic treatment

The median disease duration prior to treatment with biologics was 24 (range 0.1–132) months. The majority of the patients had previously received other immunosuppressive therapies as outlined in Table 1. The median cumulative dose of previous cyclophosphamide therapy in 21/25 patients who received it was 3.5 (range 0.5–9) g/m^2. The median daily dose of prednisolone immediately prior to treatment with biologics was 1 (range 0.14–2) mg/kg/day.

Indication for biologic therapy

The indications for therapy with biologics included failure of prior treatment to induce remission or disease relapse in 21/25 patients. The remaining 4/25 patients had flares of disease activity with high cumulative doses of cyclophosphamide leading to a clinical decision to treat with a biologic rather than more cyclophosphamide. In three of the children (Patients 2, 3 and 17), biologics were used in combination with other conventional treatment to achieve rapid remission as first-line management of critical organ or life-threatening disease. The biologic agents used, dose, duration of therapy and concomitant immunosuppressive treatment are summarized in Table 2.

The median duration of follow-up of all 25 patients was 32 (range 4–60) months. The median time to addition of an alternative biologic therapy in the seven patients this applied to was 11 (range 4–31) months. The median total duration of follow-up for these patients who received an additional biologic therapy was 39 (range 30–60) months.

Infliximab

A total of 14/25 of the patients received infliximab. The diagnoses in this group were: PAN ($n=8$); WG ($n=1$); MPA ($n=1$); and UCV ($n=4$). Infliximab was the single biologic agent used in 7/25 patients, and in the remaining seven patients was one of the two or more sequential biologics used (Patients 4, 9, 10, 18, 19, 21 and 24, Table 2 and see below). Infusions were administered intravenously at a median dose of 4 (range 3–6) mg/kg, followed by infusions at Weeks 2, 6 and then every 6–8 weeks. The median duration of therapy was 12 (range 0.25–52) months.

Rituximab

A total of 10/25 patients received rituximab. Four patients had WG; one had PAN and five had UCV. In six of these patients rituximab was the only biologic received, and in the remaining four rituximab was one of the two or more biologics used sequentially (Patients 4, 9, 18 and 19, Table 2 and see below). The commonest regimen used was two doses at 750 mg/m^2 (maximum dose 1 g) infused 14 days apart ($n=8/10$ patients). The remaining two patients received 375 mg/m^2 weekly for 4 weeks. In most cases, the rituximab infusion was accompanied by intravenous cyclophosphamide with doses varying between 350 and 500 mg/m^2 ($n=8/10$ patients). In Patients 2 and 3, rituximab combined with cyclophosphamide therapy resulted in rapid disease control and was thus followed by subsequent reduced cyclophosphamide therapy used at a dosage of 500 mg/m^2 instead of 750 mg/m^2 to consolidate the remission. Six patients continued adjunctive maintenance immunosuppressive therapy post-rituximab: this was mycophenolate mofetil (MMF) ($n=2$) (these two patients received rituximab without cyclophosphamide); AZA ($n=2$); MTX ($n=1$) and cyclosporin A (CSA) ($n=1$).

Patients receiving more than one biologic agent

Seven out of the 25 patients needed further treatment with a second biologic agent (Patients 4, 9, 10, 18, 19, 21 and 24, Table 2). The diagnoses in this patient sub-group were PAN

TABLE 1. Clinical characteristics of the patients, cumulative dose of cyclophosphamide administered, other previous therapy, daily corticosteroid dose, active organ involvement and classification of vasculitis according to Chapel Hill Consensus Criteria (CHCC), ACR criteria and the new PRES/EULAR classification criteria of paediatric vasculitis

Patient number	Clinical features	Autoantibodies	Duration of previous therapy in months	Cumulative dose of CYC, g/m^2	Daily prednisolone dose, mg/kg pre-biologic therapy	Previous therapy (DMARD other than CYC and/or PE)	Organs affected at start of biologic therapy	Vasculitis classification and system used for classification
1	Weight loss, fever, malaise, bilateral parotid swelling, nasal granulomas, saddle nose, pulmonary infiltrates, proteinuria	cANCA, PR3-38	12	3.86	0.75	AZA, MMF	C, ENT, L	1. WG (Chapel Hill Consensus) 2. WG (ACR) 3. WG (PRES classification of childhood vasculitis)
2	Malaise, weight loss, livedo reticularis, arthritis, episcleritis, haematuria, proteinuria	cANCA PR3-65	1.6	1.24	2	Nil	R	1. WG (Chapel Hill Consensus) 2. WG (ACR) 3. WG (PRES classification of childhood vasculitis)
3	Fever, malaise, arthralgia, weight loss, erythema nodosum, episcleritis, pulmonary haemorrhage	cANCA PR3-28	0.1	0.5	2	PE, IVIG	S, R, L	1. WG (Chapel Hill Consensus) 2. WG (ACR) 3. WG (PRES classification of childhood vasculitis)
4	Fever, malaise, weight loss, myalgia, epistaxis, haematuria, proteinuria, productive cough	Negative	96	8.5	1	PE, IVIG, AZA, Colchicine	C, ENT, L, R, GI	1. WG (Chapel Hill Consensus) 2. WG (ACR) 3. WG (PRES classification of childhood vasculitis)
5	Purpura, oromucosal ulceration, haemoptysis	cANCA, PR3-30	6	2	0.14	Nil	S	1. WG (Chapel Hill Consensus) 2. WG (ACR) 3. WG (PRES classification of childhood vasculitis)
6	Malaise, livedo reticularis, haematuria, proteinuria, renal failure	pANCA, MPO-39, ACL IgG 23.4, LAC negative	12	1.95	1	PE, IVIG, AZA	R, GI	1. MPA (Chapel Hill Consensus) 2. PAN (ACR) 3. MPA(PRES classification of childhood vasculitis)
7	Myalgia, arthritis, livedo reticularis, skin nodules, purpura, optic neuritis, sensorineural hearing loss, large right Sylvian haematoma and subarachnoid haemorrhage, II and III cranial nerve palsy, diarrhoea	Negative	11	4.75	0.6	Colchicine	C, GI	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis)
8	Malaise, weight loss, arthralgia, oromucosal ulceration, pyoderma gangrenosum, intestinal inflammation, nasal septum perforation	cANCA, PR3-15	4	Nil	0.7	MTX	C, S, ENT	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis)
9	Fever, weight loss, malaise, myalgia, arthritis, purpura, livedo reticularis, interstitial lung disease	ANA 1:640	26	5.7	0	CSA, MTX	C, S, J, L	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis)
10	Weight loss, malaise, erythematous rash, RP, pulmonary hypertension, diarrhoea	ANA 1:160	132	3.5	1	IVIG, AZA, Thal	S, L, PH, N	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis)
11	Weight loss, malaise, myalgia, arthralgia, livedo reticularis, peripheral ischemic ulcerative lesions, MR brain cerebral vasculitis	Negative	48	4.6	1	PE, AZA, MMF	S	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis)
12	Fever, weight loss, malaise, myalgia, arthritis, maculopapular rash	Negative	55	4.5	1.5	AZA, MMF	C, S, J, GI	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis)
13	Fever, malaise, weight loss, basal ganglia stroke, MR brain cerebral vasculitis	Negative	12	3.75	0.2	AZA	C	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis)
14	Fever, weight loss, malaise, myalgia purpura, livedo reticularis	Negative	48	3	1	PE, AZA, MMF	C, S	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis
15	Malaise, weight loss, myalgia, abdominal pain, seizure, hypertension	Negative	24	4	1	Nil	GI, N, J	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis
16	Malaise, weight loss, skin nodules, hemiparesis, confusion	Negative	12	1.75	2	AZA	C, S	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis

(continued)

TABLE 1. Continued

Patient number	Clinical features	Autoantibodies	Duration of previous therapy in months	Cumulative dose of CYC, g/m^2	Daily prednisolone dose, mg/kg pre-biologic therapy	Previous therapy (DMARD other than CYC and/or PE)	Organs affected at start of biologic therapy	Vasculitis classification and system used for classification
17	Fever, weight loss, myalgia, malaise, arthritis, purpura, multiple intestinal infarcts and perforation	Negative	60	0.5	2	MTX	C, S, GI, N	1. PAN (Chapel Hill Consensus) 2. PAN (ACR) 3. PAN (PRES classification of childhood vasculitis)
18	Fever, malaise, weight loss, myalgia, conjunctivitis, epistaxis, oromucosal ulceration, livedo reticularis, purpura	ACL IgG 59.1, LAC negative	36	3	1	PE, IVIG, AZA, MTX, Thal	C, S, J, GI, ENT	1. UCV (Chapel Hill Consensus) 2. UCV (ACR) 3. UCV (PRES classification of childhood vasculitis)
19	Fever, malaise, weight loss, myalgia, arthralgia, interstitial lung disease, pulmonary hypertension, recurrent polychondritis particularly of the pinnae	ACL IgG 38.7, LAC positive	120	4.5	1	AZA, Colchicine	C, S, L, PH, J	1. UCV (Chapel Hill Consensus) 2. UCV (ACR) 3. UCV (PRES classification of childhood vasculitis)
20	Interstitial lung disease, pulmonary hypertension	ANA 1:320, pANCA	2	Nil	1	AZA, MMF, Colchicine	L	1. UCV (Chapel Hill Consensus) 2. UCV (ACR) 3. UCV (PRES classification of childhood vasculitis)
21	Weight loss, blisters, purpura, arthritis, oromucosal ulceration, hypertension, diarrhoea, abdominal pain	Negative	12	2.9	2	Mesalazine	C, S, J, GI	1. UCV (Chapel Hill Consensus) 2. UCV (ACR) 3. UCV (PRES classification of childhood vasculitis)
22	Weight loss, malaise, livedo reticularis, skin infarcts, skin nodules, arthritis, diarrhoea, abdominal pain	cANCA, PR3-476	96	2.23	1	AZA, MTX, MMF, dapsone	S	1. UCV (Chapel Hill Consensus) 2. UCV (ACR) 3. UCV (PRES classification of childhood vasculitis)
23	Weight loss, malaise, myalgia, arthritis, erythematous rash, episcleritis, diarrhoea	Negative	12	0.93	1	AZA, MMF	S, O, J	1. UCV (Chapel Hill Consensus) 2. UCV (ACR) 3. UCV (PRES classification of childhood vasculitis)
24	Fever, weight loss, malaise, myalgia, arthritis, erythema nodosum, vasculitic rash, oral ulcers	Negative	96	Nil	0.65	AZA, colchicine	C, S, J	1. UCV (Chapel Hill Consensus) 2. UCV (ACR) 3. UCV (PRES classification of childhood vasculitis)
25	Orogenital ulceration, skin rash, fever	ANA 1:160	84	Nil	1	AZA, MMF Thal, colchicine	S, G	1. UCV (Chapel Hill Consensus) 2. UCV (ACR) 3. Behçet's disease (PRES classification of childhood vasculitis)

Dx: diagnosis; CYC: cyclophosphamide; Thal: thalidomide; PE: plasma exchange; IVIG: intravenous immunoglobulin; S: skin; L: lungs; R: renal; GI: gastrointestinal; J: joints; C: constitutional; N: neurology; O: ocular; PH: pulmonary hypertension; G: genitalia; CVS: cardiovascular; ACL (reference range 0–17 GPL U/l); PR3 (reference range 0–10 EU/ml); MPO (reference range 0–10 EU/ml).

($n=2$); WG ($n=1$); and UCV ($n=4$). In 6/7 cases, infliximab was the first biologic used and was switched to another agent because of failure to control disease activity. Rituximab was the commonest second biologic used ($n=3$ patients); in the remaining patients, the second biologic after infliximab was etanercept, adalimumab or anakinra (all $n=1$). Patient 18 received three biologics sequentially: infliximab (one dose that resulted in deterioration in oromucosal and skin vasculitis), followed by rituximab and eventually anakinra. The median duration of follow-up of this subgroup was 39 (range 30–60) months.

Other biologic therapy

Four patients were treated with etanercept at a dose of 0.4 mg/kg subcutaneously twice a week (maximum dose 25 mg) as the first-line biologic agent (Patients 5, 15, 16 and 17, Table 2) and Patient 21 received etanercept following infliximab therapy. Two patients received adalimumab. Patient 25 (Table 2) had Behçet's disease and was treated with adalimumab (40 mg subcutaneously every 14 days) as the first-line biologic. Patient 10 with PAN received adalimumab (again at a dose of 40 mg every 14 days) after escaping initial efficacy from infliximab.

Overall therapeutic response

Overall, there was a significant reduction in the BVAS score in all patients from a median of 8.8 (range 5–32) at the start of therapy with biologic to 4 (range 0–19) at median 32 months follow-up ($P=0.003$; Fig. 1A). Nine out of the 25 patients had achieved complete remission at the time of latest follow-up as indicated by a BVAS of 0.

Figure 1B summarizes the change in baseline daily prednisolone dose for all 25 patients before and after biologic therapy at follow-up. There was a significant reduction in median daily prednisolone requirement from 1 (range 0.2–2) to 0.25 (range 0–1) mg/kg/day at 31 months ($P=0.000$).

The ESR fell from a median of 56 (range 3–145) to 13 (range 0–152) mm/h at median of 31-months follow-up, although this observation was not statistically significant ($P=0.195$). Similarly, the median CRP fell (non-significantly) from a

TABLE 2. The biologic agents used including dose and duration of therapy, concomitant immunosuppressive treatment and adverse events

Patient	Classification	Biologic agent[a]	Dose	Concomitant immunosuppressive therapy	Adverse events
1	WG	Rituximab	750 mg/m^2 × 2 (14 days apart)	MMF 1 g twice a day (1.8 mg/m^2/day)	Paronychia 2 months post-rituximab
2	WG	Rituximab	750 mg/m^2 × 2 (14 days apart)	CYC 375 mg/m^2 with rituximab followed by 4 monthly pulses of 500 mg/m^2	Nil
3	WG	Rituximab	750 mg/m^2 × 2 (14 days apart)	CYC 375 mg/m2 with rituximab followed by 4 monthly pulses of 500 mg/m^2	Nil
4	WG	Infliximab	5 mg/kg three doses	CSA 5 mg/kg/day	Pseudomonas UTI and concurrent pneumonia 9 months after infliximab was stopped and 7 months post-rituximab
		Rituximab	375 mg/m^2 weekly for 4 weeks	iv CYC 500 mg/m^2 monthly (first pulse with rituximab and then 5 further monthly pulses)	
5	WG	Etanercept	25 mg twice a week—discontinued after 22 months	MTX 15 mg/m^2 once a week	Nil
6	MPA	Infliximab	3 mg/kg one dose	iv CYC 600 mg/m^2 6 monthly pulses, AZA 2 mg/kg/day	Shingles after single infliximab infusion
7	PAN	Infliximab	3 mg/kg 6 weekly continuing	AZA 1 mg/kg/day	Nil
8	PAN	Infliximab	5 mg/kg four doses	MTX 15 mg/m^2 once a week	Nil
9	PAN	Infliximab	3 mg/kg four doses	MTX 15 mg/m^2	Nil
		Rituximab	750 mg/m^2 × 2 (14 days apart)	CYC 500 mg/m^2 with rituximab	
10	PAN	Infliximab	3 mg/kg five doses 6 mg/kg three doses	MTX 10 mg/m^2	Staph epidermis sepsis post-second infliximab infusion
		Adalimumab	40 mg s.c. every fortnight		
11	PAN	Infliximab	3 mg/kg six doses	MMF 1 g twice a day (750 mg/m^2/day)	Nil
12	PAN	Infliximab	5 mg/kg six doses	AZA 1 mg/kg/day	Nil
13	PAN	Infliximab	6 mg/kg four doses	AZA 2 mg/kg/day	Nil
14	PAN	Infliximab	5 mg/kg two doses fortnight apart	iv CYC 500 mg/m^2 6 monthly pulses (one dose prior to infliximab)	Cerebral abscesses following two infliximab infusions and first CYC
15	PAN	Etanercept	0.8 mg/kg/week	AZA 2 mg/kg/day	Bowel perforation a month after starting etanercept
16	PAN	Etanercept	0.8 mg/kg/week	Nil	Nil
17	PAN	Etanercept	0.8 mg/kg/week	Nil	Nil
18	UCV	Infliximab	6 mg/kg nine doses	AZA 1 mg/kg/day	Skin erythema at injection site with anakinra
		Rituximab	375 mg/m^2 for 4 weeks	iv CYC 500 mg/m^2 monthly with rituximab	
		Anakinra	1 mg/kg s.c. weekly continuing		
19	UCV	Rituximab	750 mg/m^2 × 2 (14 days apart)	iv CYC 500 mg/m^2 6 monthly pulses started with rituximab	Mild headache with second rituximab infusion; fungal nail infection 6 months after starting infliximab
		Infliximab	6 mg/kg 6 weekly continuing	AZA 2 mg/kg/day started post-CYC	
20	UCV	Rituximab	750 mg/m^2 × 2 (14 days apart)	iv CYC 500 mg/m^2 6 monthly pulses	Nil
21	UCV	Infliximab	3 mg/kg six doses	AZA 1 mg/kg/day	Nil
		Etanercept	0.4 mg/kg twice a week/5 months		
22	UCV	Rituximab	750 mg/m^2 × 2 (14 days apart)	CYC 500 mg/m^2 with rituximab	Nil
23	UCV	Rituximab	750 mg/m^2 × 2 (14 days apart)	MMF 750 mg am/500 mg pm (1 g/m^2/day)	Nil
24	UCV	Infliximab	3 mg/kg six doses	AZA 2 mg/kg/day	Skin erythema at injection site with anakinra
		Anakinra	2 mg/kg daily for 12 months		
25	Behçet's disease	Adalimumab	40 mg once a fortnight	Nil	Nil

LV: leucocytoclastic vasculitis; CYC: cyclophosphamide; iv: intravenous; BMT: bone marrow transplantation. [a]For those patients receiving more than one biologic agent, the agents are listed in the order that the patient received them sequentially.

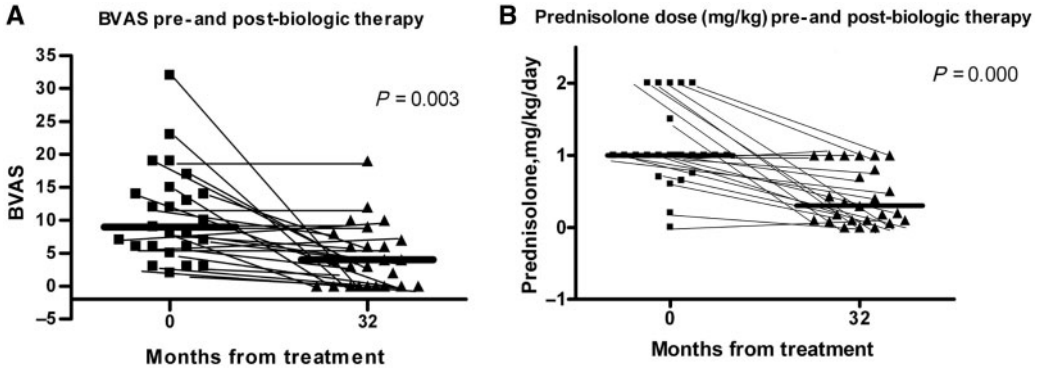

FIG. 1. Overall response to treatment with biologic therapy. (**A**) Change in BVAS before ($T=0$) and after (median time to latest follow-up 32 months) treatment with infliximab ($n=7$), rituximab ($n=6$), etanercept ($n=4$), adalimumab ($n=1$) or multiple biologic agents sequentially ($n=7$) for a total of 25 patients with PSV. (**B**) Daily oral corticosteroid dose (mg/kg/day) in response to therapy with biologics. Horizontal lines represent median values. Changes in paired continuous variables were compared using the Wilcoxon signed ranks test. *P*-values < 0.05 were considered significant.

median of 17 (range 3–71) at the start of treatment to 7 (range 3–152) mg/l at the time of follow-up ($P = 0.082$).

Therapeutic response to infliximab

Figure 2A summarizes the change in BVAS in 13 patients treated with infliximab. Patient 20 who had rituximab prior to infliximab was excluded from the analysis. The median BVAS for this subgroup fell significantly from 8 (range 2–15) to 6 (range 0–12); $P = 0.038$ at the time of median follow-up of 11 (range 4–37) months.

Overall, there was a significant decline in the median daily prednisolone dose in this group before and after infliximab. The daily prednisolone dose was 1 (range 0.6–2) mg/kg/day, and fell to 0.7 (range 0–2) mg/kg/day following infliximab therapy ($P = 0.018$) (Fig. 2B).

There was no significant change in the ESR of the patients treated with infliximab; Similarly, there was no significant change for the CRP (data not shown).

Therapeutic response to rituximab

For 10 patients treated with rituximab, the BVAS fell significantly ($P = 0.028$) from 9 (range 3–32) to 4 (range 3–12) at median follow-up of 23 (range 6–46) months (Fig. 3A). Furthermore, the median daily corticosteroid dose fell significantly from 1 (range 0.3–2) to a median of 0.4 (range 0.18–1) mg/kg/day ($P = 0.008$) (Fig. 3B). The median ESR fell non-significantly from 64 (range 3–128) to 38 (range 6–139) mm/h ($P = 0.5$). Similarly, there was no significant change in median CRP in response to rituximab (data not shown).

B-cell depletion and immunoglobulin levels following rituximab

All 10 patients who received rituximab therapy depleted their peripheral B cells within 2 weeks as defined by peripheral blood CD19 counts of 0% using routine clinical flow cytometric analysis. B-lymphocyte regeneration after therapy with rituximab occurred in four of the patients at a median of 17 (range 8–24) months. Two of the 10 patients who had received rituximab remained B lymphocyte depleted at a median follow-up of 23 (range 6–46) months. Of the remaining four patients, data regarding B-cell return was incomplete because one patient died (Patient 9), one patient underwent bone marrow transplantation (Patient 18) and two were transitioned to adult care at other centres. Out of the 6/10 patients, where data were available, no patient developed hypogammaglobulinaemia at the time of latest follow-up.

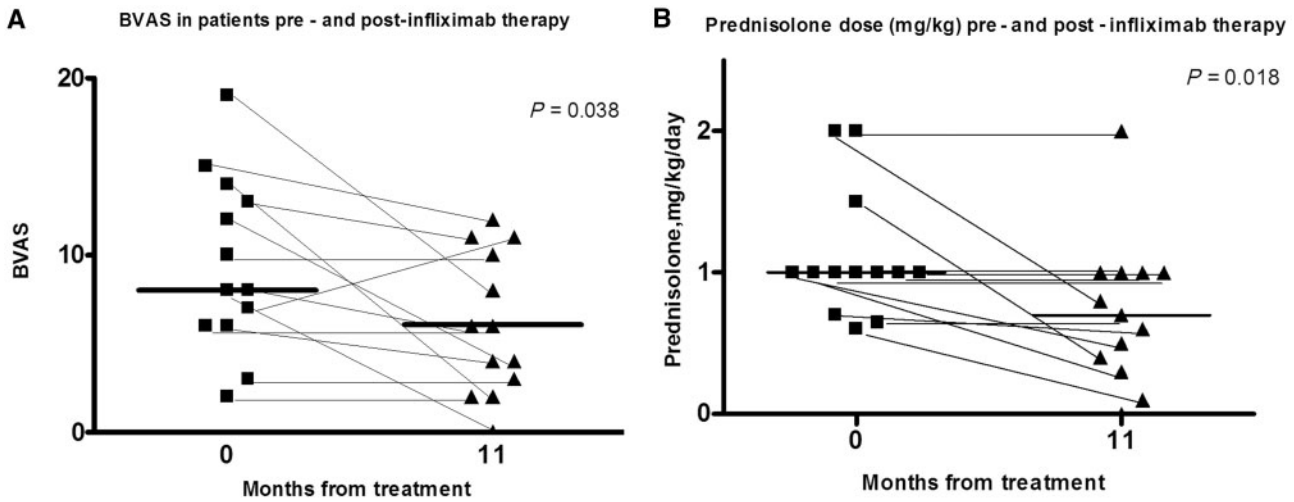

FIG. 2. Response to treatment with infliximab. (**A**) Change in BVAS before ($T = 0$) and after (median time to latest follow-up 11 months) treatment with infliximab for ($n = 13$) patients with PSV. (**B**) Daily oral corticosteroid dose (mg/kg/day) in response to therapy with infliximab. Horizontal lines represent median values. Changes in paired continuous variables were compared using the Wilcoxon signed ranks test. *P*-values < 0.05 were considered significant.

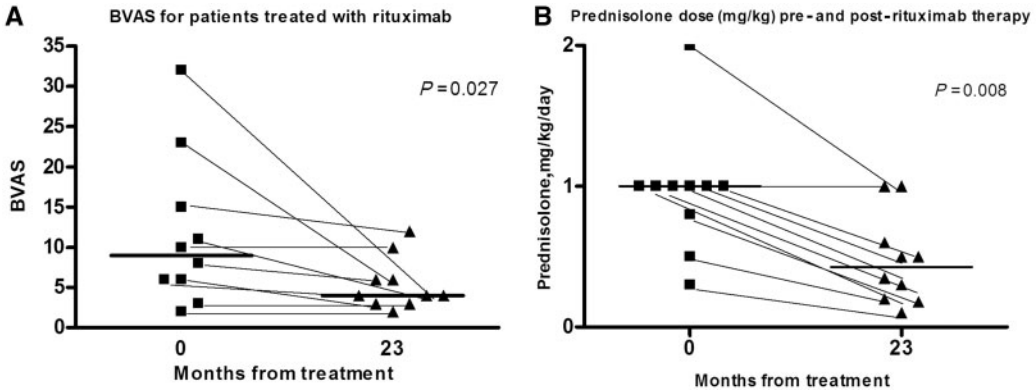

FIG. 3. Response to treatment with rituximab. (**A**) Change in BVAS before ($T = 0$) and after (median time to latest follow-up 23 months) treatment with rituximab for ($n = 10$) patients with PSV. (**B**) Daily corticosteroid dose (mg/kg/day) in response to therapy with rituximab. Changes in paired continuous variables were compared using the Wilcoxon signed ranks test. *P*-values < 0.05 were considered significant.

Therapeutic response in patients receiving more than one biologic agent

Subgroup analysis of the seven patients that required treatment with a second biologic agent demonstrated that the median BVAS decreased non-significantly from 10 (range 6–19) at the initiation of treatment with infliximab ($n=6$) or rituximab ($n=1$) to 6 (range 2–11) at 11 months. Following addition of an alternative biologic agent at median time 11 months [rituximab ($n=3$); infliximab, etanercept or anakinra, all $n=1$, respectively), the BVAS fell from median of 6 (range 2–11) to 4 (range 0–4); (Fig. 4A, available as supplementary data at *Rheumatology* Online). For the six patients who converted from infliximab to another agent, the median washout period between stopping infliximab and addition of a second agent was 3.5 (range 1–18) months.

The daily prednisolone dose was reduced (non-significantly) from 1 (range 0–2) to 0.8 (range 0.3–2) mg/kg/day immediately prior to the change to an alternative biologic agent at median 11 months. There was a further significant fall in the daily prednisolone dose to a median of 0.3 (range 0–0.8) mg/kg/day at the latest follow-up (median 39 months). The overall decrease in the dose of corticosteroids for this group of patients from the start of treatment with a biologic agent to the latest follow-up is summarized in Fig. 4B (available as supplementary data at *Rheumatology* Online).

In this group, the ESR remained high at a median of 56 (range 17–128) mm/h ($P=1.0$) at the time of switch to alternative biologic therapy. Following a switch in therapy, the ESR demonstrated a modest but non-significant decline to a median of 18 (range 1–139) mm/h; $P=0.463$). A similar result was obtained for CRP (data not shown).

Adverse events relating to biologic therapy

Adverse events comprised either infusion reactions or infections and are summarized in Table 2. Mild infusion reactions affected 3/25 patients. These were headache during rituximab infusion ($n=1$, Patient 19) and local skin erythema and pain at the injection site for both of the children receiving anakinra (Patients 18 and 24).

There were six significant infectious episodes post-biologic therapy in 25 (24%) of the patients, including bacterial ($n=4$), fungal ($n=1$) and viral ($n=1$) infections. One patient (Patient 6) developed shingles after a single infusion of infliximab. One patient (Patient 4) developed a *Pseudomonas* urinary tract infection (UTI) and concurrent pneumonia. That patient had received both infliximab (discontinued 9 months prior to infections) and rituximab treatment (discontinued 7 months prior) for WG. She also had a renal transplant and was receiving concurrent immunosuppressive therapy with CSA. One patient (Patient 10) with a central venous catheter *in situ* developed *Staphylococcus epidermidis* sepsis following administration of two doses of infliximab. Patient 14 with PAN developed cerebral abscesses after two doses of infliximab and a single infusion of intravenous cyclophosphamide. This patient had multiple areas of intestinal infarction and perforation secondary to vasculitis. One patient with WG (Patient 1) developed paronychia 2 months after receiving rituximab treatment. Patient 19 with UCV developed a fungal nail infection on infliximab (prior to this he had received rituximab). Patient 15 with PAN developed bowel perforation while on etanercept; although this was interpreted to be due to the primary disease the drug was stopped.

Clinical outcome

The mortality rate was 4% with one patient aged 8 years with UCV who died from respiratory failure from progressive interstitial lung disease and severe pulmonary hypertension 8 months after treatment with rituximab.

Two patients with AAV (Patients 4 and 6) had a renal transplantation for end-stage renal failure. Patient 18 underwent an allogeneic matched unrelated donor bone marrow transplant (BMT) 6 years after she was diagnosed with UCV, and after failing conventional therapy and three different biologic agents. She had no major complications following transplantation and has fully engrafted, with disease in complete remission and off all immunosuppressive therapy. Patient 19 had persistent moderate pulmonary hypertension requiring treatment with nifedipine and sildenafil. During the course of their disease, 20% of the patients (Patients 7, 11, 13, 15 and 16) had permanent neurological sequelae following cerebral vasculitis. The neurological insult occurred prior to therapy with biologics in all five patients.

Discussion

Our retrospective study describes the largest cohort of paediatric patients with PSV treated with biologic therapy, and adds to the limited data available from previously reported cases [15–17]. Although patients from three centres are described, the majority of cases (21/25) were from GOSH.

Overall, sustained clinical improvement in disease activity (although not complete long-term disease remission) was achieved for the majority of the patients included in our study, as illustrated by the significant decline in the median BVAS at the time of latest follow-up at a median of 32 months (Fig. 1A). In this study, a total of 7 out of 25 (28%) patients required treatment with a second (or in the case of Patient 18, a third) biologic agent sequentially, because of severe ongoing disease activity. Such additional biologic therapy resulted in overall sustained disease improvement in these patients (Fig. 4A, available as supplementary data at *Rheumatology* Online), although Patient 18 subsequently failed to respond to three biologic agents, and underwent allogeneic BMT with good outcome.

Our results are encouraging although an important limitation of this retrospective clinical observation is that the disease activity was assessed using a modified BVAS that has never been formally validated in children. Moreover, clinicians were not blinded when applying the BVAS scores retrospectively. The BVAS is a validated clinical scoring index for the prospective assessment of vasculitic disease activity and is widely used in clinical trials of adults with PSV, with an established track record in this context [22–25]. That said, the criteria included within the BVAS are also relevant to vasculitic syndromes of childhood, and the BVAS modifications used in the present study relate mainly to the inclusion of age-specific reference ranges for laboratory-based BVAS items (available as supplementary data at *Rheumatology* online). BVAS, despite its limitations, is regarded by many as a robust tool (but by no means the only one) for the assessment of vasculitic disease activity [26]. In the past, we demonstrated good correlation of this version of the BVAS with endothelial microparticles [25], a novel and increasingly used biomarker of endothelial injury in children and adults with vasculitis [27]. We also have recently validated this tool against another biomarker of vasculitis in children and adults' circulating endothelial cells [28].

We additionally demonstrated a significant reduction in daily prednisolone requirement following therapy with infliximab, rituximab or sequential poly-biologic therapy (Figs 1B, 2B, 3B and online Fig. 4B, available as supplementary data at *Rheumatology* Online). This change is arguably a more objective means of assessing efficacy retrospectively, and of direct clinical relevance to young patients with PSV.

Of note is that the majority of the patients described did not have a significant reduction in their acute phase reactants at follow-up, which was an unexpected observation. This may indicate that only partial remission was achieved in some patients. In support of this was that although overall BVAS fell in many

TABLE 3. Recommendations for the indication and choice of biologic therapy for PSV of the young based on published experience

Vasculitis type	Indication for biologic agent	Proposed first choice of biologic agent
ANCA-associated vasculitis	Critical organ or life-threatening disease that has failed to respond to standard vasculitis therapy. OR concerns regarding cumulative CYC dose.	Rituximab or other B-cell depleting monoclonal antibody
Polyarteritis nodosa	Failed therapy with standard agents OR concern regarding cumulative CYC dose	Rituximab or anti-TNF-α[a,b]
Behçet's disease	Recalcitrant and severe disease; alternative to thalidomide	Anti-TNF-α (infliximab, adalimumab or etanercept)

IVIG: intravenous immunoglobulin. [a]Authors have more experience with infliximab than etanercept for PAN, although etanercept has been used in individual cases of childhood PAN [43]. [b]No firm recommendation is made regarding first choice of biologic for PAN.

instances, it did not reach 0 at follow-up in 64% ($n = 16/25$) of the patients.

In regards to efficacy of infliximab in our patients, our results are broadly similar to the experience of using infliximab in adult patients with vasculitis. Infliximab demonstrated efficacy in obtaining initial disease control but allowed corticosteroid taper in a minority of patients (Fig. 2). Forty-six per cent (6/13) of the patients who received infliximab as the first biologic agent required a switch to a second agent to control disease activity.

Etanercept and adalimumab were used in a limited number of cases (five and two patients, respectively). Adalimumab, in particular, demonstrated efficacy in the two patients receiving that agent. Currently, based on the lack of adjunctive efficacy of etanercept demonstrated in a clinical trial in adults with WG [24], there is a perception that this agent may not be the preferred choice of TNF-α blockade in children or adults with PSV [29–34]. The results of our study are unfortunately too preliminary to guide clinicians as regards to the choice of anti-TNF-α agent best suited for the treatment of PSV in the young.

We used rituximab in 10 patients usually in combination with cyclophosphamide, similar to the approach in SLE [14]. Overall, this was associated with improvement in BVAS, and allowed corticosteroid taper (Fig. 3A and B). Five of these patients had ANCA positivity (PR3 ANCA positive), but importantly efficacy of rituximab was not confined to the ANCA-positive patients. For Patients 2 and 3 with WG, rituximab in combination with cyclophosphamide was effective in inducing remission at the start of their illness and resulted in shorter courses and lower doses of cyclophosphamide required to consolidate the remission. Rituximab therapy has been assessed in adult patients with AAV in seven different reports [35–41]. In the six studies with favourable responses, complete remission occurred in 50 out of the 54 patients. In the single study that demonstrated poor efficacy, patients with retro-orbital granulomas, an uncommon and often recalcitrant manifestation of WG, were included and the study used a different dosing regimen for rituximab than that reported here [36].

We report an overall infectious complication rate of 24% for our patient group. The most severe infectious complications occurred in those patients receiving infliximab and comprised shingles, sepsis with pseudomonas or *Staphylococcus epidermidis* and cerebral abscess formation (not requiring neurosurgical drainage hence no organism identified). We cannot attribute all these infectious complications solely to blockade of TNF-α, since previous and concomitant immunosuppression- and disease-related factors undoubtedly contributed, but our observations taken at face value do indicate significant infectious risk associated with the use of infliximab (and other anti-TNF-α therapy) in this patient cohort.

There was significant overall morbidity and one death in our series. Much of this morbidity, which included critical organ damage such as pulmonary hypertension, permanent neurological sequelae, requirement for renal transplantation and BMT for failed therapy, reflected the severe nature of the vasculitic disease represented by this series of patients and disease-related damage accrued prior to starting biologic therapy.

In summary, we present our collective experience of the use of biologics in treatment of PSV of the young. Although this is the largest series of such paediatric cases described, interpretation is limited as this was a retrospective study with relatively limited patient numbers. There is no doubt that biologic therapies provide a potent addition to our therapeutic armamentarium for systemic vasculitis, particularly for those failing conventional therapy. On the basis of our data, we cannot yet firmly endorse specific biologic therapy for individual vasculitic syndromes (with the exception perhaps of Kawasaki disease where infliximab is increasingly used) [42]. That said, based on our experience and that of others we can make some preliminary recommendations as set out in Table 3. Until we undertake multi-centre randomized controlled trials of these agents, using agreed protocols in children with PSV, therapeutic decisions will remain based on anecdotal evidence. Thus, further standardized collection of data from multiple centres regarding the efficacy and safety of biologic therapy for recalcitrant vasculitis of the young will be required for ongoing monitoring of safety and efficacy in this context.

Rheumatology key messages

- Biologic therapies provide a potent addition to our therapeutic armamentarium for systemic vasculitis.
- Multicentre standardization of treatment protocols and data collection is required to inform future clinical trials.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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