Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents

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Received on October 31, 2011; accepted in revised form on March 26, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 70): S139-S161.

Key words: biologic agents, large-vessel vasculitis

For list of abbreviations used in the text, see page S157.

Competing interests: none declared.

ABSTRACT

Objective. *To provide recommendations on behalf of the Italian Society for Rheumatology for the off-label use of biologic agents in the treatment of large-vessel vasculitis.*

Methods. *A panel of experts performed a literature search and selected the evidence relevant to the topic. The following five large-vessel vasculitides were considered: giant cell arteritis, Takayasu arteritis, primary angiitis of the central nervous system, Cogan's syndrome, and Adamantiades-Behçet's disease.*

Results. *A consensus was achieved regarding the indication of biologic agents for the treatment of large-vessel vasculitis. Levels of evidence were assigned to the papers retrieved, and the strength of the recommendations was graded according to the levels of evidence.*

Conclusions. *These recommendations may be used for guidance in deciding which patients with large-vessel vasculitis should receive biologic therapy. Further updates of these recommendations may be published on the basis of the results of new clinical studies and of data from post-marketing surveillance.*

Introduction and aim

The primary large-vessel vasculitides are idiopathic inflammatory vasculopathies involving the large vessels of the body, *i.e.* those with a caliber greater than 150 μm (1). Five primary vasculitides can affect the large vessels: giant cell arteritis (GCA), Takayasu arteritis (TA), primary angiitis of the central nervous system (PACNS), Cogan syndrome, and Adamantiades-Behçet disease (ABD). GCA, TA, PACNS and Cogan syndrome involve preferentially or exclusively large vessels, while ABD can involve vessels of any caliber.

The aim of this paper was to review the published evidence on the treatment of large-vessel vasculitis with biological agents, and to formulate recommendations for their use in clinical practice on the basis of the published evidence.

Methods

We searched PubMed (search until January 2012) using the following key words and Boolean operators: ("infliximab"[Substance Name] OR "TNFR-Fc fusion protein"[Substance Name] OR "etanercept" OR "adalimumab"[Substance Name] OR "Tumour Necrosis Factor-alpha/antagonists and inhibitors"[MeSH] OR "golimumab" OR "tocilizumab" OR "rituximab" OR "Interferon Alpha-2a" OR "Interferon Alpha-2b" OR "Interferon Alpha-2c") AND ("Vasculitis, Central Nervous System"[Mesh] OR "Giant Cell Arteritis"[Mesh] OR "Takayasu Arteritis"[Mesh] OR "Behcet Syndrome"[Mesh] OR "Cogan syndrome"). We retrieved 308 references. The retrieved papers were included in our analysis if they were pertinent to the diseases and treatments considered, if they were in English, if the diagnosis was reliably established, if the cases reported were not paediatric (except for adult patients with onset of disease manifestations in childhood), and if sufficient information could be extracted with regard to treatment. Editorials, review articles, authors' replies and, broadly speaking, manuscripts not reporting treatment of patients have not been considered for analysis.

Levels of evidence were assigned to the papers retrieved, and the strength of the recommendations graded according to the levels of evidence (2). However, in these recommendations we have also taken into account the perceived global

cost/benefit ratio, in line with the recommendations and guidelines by other international societies (3).

Adamantiades-Behçet's disease

Adamantiades-Behçet's disease (ABD), also known as Behçet's disease or Behçet's syndrome, is a vasculitis involving blood vessels of all sizes characterised by oral aphthae often associated with genital aphthae with frequent skin lesions and variable involvement of other organs (4). A limited number of RCT has been carried out in ABD, but to date its treatment remains largely empirical. Despite the panoply of medications used to treat ABD, a number of patients fail to respond adequately to treatment, or require unacceptably high doses of GC to maintain remission.

There are several studies on the use of biological agents (mainly TNF-α inhibitors and IFN-α) in ABD patients, many of whom had refractory disease, with encouraging results. The rationale for using these agents has been discussed elsewhere (5). Herein, we have reviewed the published literature on the management of ABD patients with biological agents, and formulated recommendations for their use on the basis of the existing evidence.

Randomised controlled trials in Adamantiades-Behçet's disease

Only three RCTs testing the efficacy of biological agents have been carried out in ABD patients. One trial focused on mucocutaneous ABD (6), one looked at a variety of disease manifestations (7), and another aimed primarily at assessing the efficacy of IFN-α in preventing the development of inflammatory eye disease (8). All these trials have included patients fulfilling the classification criteria by the International Study Group of Behçet's Disease (9), but excluded patients with severe organ involvement at study entry. One of this trials (8) has been the object of a bitter controversy because of the suspicion of fabrication of data by the first author (10). However, since the first author has subsequently been cleared of this suspicion by a verdict of the Turkish supreme court (11), we decided to include this RCT in our analysis.

– Randomised controlled trials of etanercept for Adamantiades-Behçet's disease

ETA is the only TNF-α inhibitor that has been formally tested in a RCT (6). Forty male patients with ABD characterised by mucocutaneous lesions, arthritis, or both, were randomised to receive ETA 25 mg subcutaneously twice weekly or placebo for four weeks. ETA did not prove superior to placebo in affecting the pathergy test or the skin reaction to injection of urate crystals, which were the primary end points of the trial. However, ETA significantly decreased the number of oral ulcers and nodular lesion with a trend for a reduction of genital ulcers and arthritis attacks. The small sample size and the relatively infrequent occurrence of genital ulcers and arthritis may explain why the effects of ETA on these manifestations did not reach statistical significance.

– Randomised controlled trials of interferon-α for Adamantiades-Behçet's disease

The efficacy of IFN-α in ABD patients has been investigated in two RCT. In one trial, 50 ABD patients with a variety of disease features were randomised to IFN-α2a or a to matched placebo given subcutaneously at a dose of 6 million units thrice weekly for three months (7). Fifteen of the 23 INF-α2a treated patients responded to treatment compared to only 3 of 21 patients in the placebo arm. More specifically, IFN-α2a significantly reduced the duration of oral ulcers, the frequency of genital ulcers and papulo-pustular lesions, and the frequency and duration of ocular attacks. Only mild adverse events were reported, among which an IFN-α-related flu-like syndrome was the most common one.

In another RCT, 135 patients treated with colchicine 1.5 mg/day and benzathin penicillin 1.2 million units every three weeks were randomised to receive INF-α2b or placebo every other day for six months (8). Treatment with IFN-α2b significantly reduced the attack rates of oral ulcers, genital ulcers, skin lesions, arthritis, vascular events, and ocular inflammatory. On a note of caution, because of the small number of patients who had vascular events during the study, a type I error can not be ruled out for this particular manifestation. The number of patients with neurological manifestations was even smaller, and thus the two study groups were not formally compared for the development of central nervous system disease. Only mild adverse events were reported, among which an IFN-α-related flu-like syndrome was the most common one.

Open-label studies, retrospective reviews, case series and case reports of biological agents in Adamantiades-Behçet's disease

As we have mentioned above, only three RCT have been carried out in ABD, which do not encompass the entire spectrum of the manifestations of ABD. Similarly, the populations they enrolled are not always representative of "real-life" patients because of restrictive inclusion criteria. In particular, all these trials excluded patients with severe organ involvement, *i.e.* those who are most in need of aggressive treatment. For these reasons, it is necessary to consider also uncontrolled studies to gain a proper understanding of the efficacy of biological agents in ABD. Herein, we have reviewed the literature on published uncontrolled observations in ABD. The results (shown in detail in Table I) demonstrate efficacy of both TNF-α inhibitors and IFN-α "across the board" in a large variety of disease manifestations, including oral and genital ulcers, skin lesions, uveitis, retinal vasculitis, parenchymal lesions of the central nervous system, arthritis, and gastrointestinal ulcers. In contrast, there is only anecdotal data on the use of biological agents in patients with vascular disease (aneurysms and thrombophlebitis).

– Uncontrolled studies on TNF-α inhibitors (not reported in Table I)

The efficacy of TNF-α inhibitors in the treatment of ABD has been confirmed by a recent review of the data on 369 patients who received such agents (12). More specifically, robust clinical responses were noted in 90% of

Tab. I. Case reports and case series on the use of biological agents in Adamantiades-Behçet's disease.

Ref.	Pts	N/R	Organ involved	Study Drug (other drugs)	F'up	Outcome
			Mucocutaneous lesions			
				Infliximab		
(78)	1	R	Oral ulcers	IFX 5 mg/kg at week 0, 2, 6 then ~8-weekly (PDN 25 mg tapering, MTX)	~94/52	Response
(79)	1	R	Oral ulcers	IFX 5 mg/kg at week 0,2,4,8 (GC)	8	Remission after 2nd infusion
(80)	5	R	Oral ulcers	IFX 5-10 mg/kg at 0, 2, 6, 10 (GC and colchicine allowed)	median 52 days	Resolved in 2/2 (5 mg/kg) and 2/3 (10 mg/kg)
(81)	5	NR	Oral ulcers	IFX 3 mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter	13-39	All improved
(82)	1	R	Oral ulcers	IFX 5 mg/kg at day 0, 15, 45, monthly (Cy-A, PDN)	~2 years	Remission (but developed aortic aneurysm after 2 years)
(83)	5	R	Oral ulcers	IFX 5 or 10 mg/kg at week 0,2,6,10 (GC rescue treatment allowed)	14/52	Efficacy assessed at 14/52 Resolution in 4/5 cases
(84)	1	N	Oral ulcers	IFX 3 mg/kg 3 infusion over 4/52 (PDN 60 mg tapering to 10 mg)	1 year	CR
(85)	1	R	Oral ulcers	IFX 5 mg/kg at day 1, 30, then 8-weekly (GC, colchicine)	11/12	Resolution within 10 days
(86)	1	R	Oral ulcers	IFX 3 mg/kg at week 0, 2, 6, 12 then 8-weekly (GC, MTX 15 mg/week)	12/12	Response within 2 days
(74)	1	R	Oral ulcers	IFX 3 mg/kg every 8 weeks (MTX 12.5 mg/week)	~ 1 year	Remission
(87)	1	R	Oral ulcers	IFX 3 mg/kg at 0, 2, 6, then 8-weekly (colchicine, AZA)	NS	Resolved two weeks after the first infusion
(88)	2	R	Oral ulcers	IFX 3-5 mg/kg 2-3 infusions "on demand" (GC)	~2 years	Resolved within a few days
(89)	1	R	Oral ulcers	IFX 10 mg/kg doses 1 month apart (PDN 15 mg/day, MTX 15 mg/week)	13/12	Resolved after the second IFX infusion
(90)	1	R	Oral ulcers	IFX 5 mg/kg at week 0, 2, 6 (colchicine)	NS	Marked improvement after 1/52, resolved after 3/52
(91)	1	N	Oral ulcers	IFX 5 mg/kg at week 0, 2, 6, 14, 22, then 8-weekly	12/12	Resolved within 8 days
(92)	1	R	Oral ulcers	IFX 5 mg/kg at week 0, 2, 6 then 8-weekly → 3 mg/kg every 3 months (PDN, Cy-A, AZA)	3.5 years	Remission after the 3rd infusion. Cy-A withdrawn and GC tapered off. Follow-up reported in (93)
(94)	7	5R, 2N	Oral ulcers	IFX 5 mg/kg mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter (2 GC, 7 AZA)	32/12	Response noted in 4 out of 7 patients
(95)	5	R	Oral ulcers	IFX 3-5 mg/kg at 0-2-6 weeks then 8-weekly (10 MTX, 8 colchicine, 2 AZA, 5 mesalazine, 2 sulfasalazine, 6 GC)	24/12	Resolved in all patients affected
(96)	2	R	Oral ulcers	IFX 3 mg/kg every 4 weeks then 5 mg/kg every 8 weeks (1 patient) and 3 mg/kg (1 patient) (GC)	up to 21/12	Gradual improvement culminating in remission in one patient and rapid (6 weeks) improvement in the other patients
				Adalimumab		
(96)	1	R	Oral ulcers	ADA 40 mg eow (GC, AZA, MTX)	~18/12	Partial response with reduced frequency of attacks and of number of ulcers
(97)	5	R	Oral ulcers	ADA (after a course of IFX) (3 GC, 4 various IS)	562 days	Three complete and two partial responses
(98)	1	R	Oral ulcers	ADA (after IFX) 40 mg eow (GC)	2/12	Resolution after the first injection
(99)	1	R	Oral ulcers	ADA 160 mg followed by 80 mg and then 40 mg eow (GC, colchicine)	60 weeks	Response to ADA treatment
				Etanercept		
(100)	2	R	Oral ulcers	ETA 25 mg twice weekly	NS	1 CR, 1 treatment failure
(101)	1	R	Oral ulcers	ETA 25 mg twice weekly for 3/12 followed by IFX 0,2 and then every 8 weeks (MTX 7.5 mg/week)	1 year	ETA not effective. Resolution after the first infusion of IFX
(102)	1	R	Oral ulcers	ETA 25 mg twice weekly (PDN final dose 5 mg/kg)	1 year	Responded, CR within 1/12
(103)	2	N	Oral ulcers	ETA 25 mg twice weekly	>6/12	Resolved within 3-5 weeks, relapse upon discontinuation
(104)	1	R	Oral ulcers	ETA 25 mg twice weekly (PDN 25 mg/day tapering)	NS	Resolution in 4/52
(105)	1	N	Oral ulcers	ETA 25 mg twice weekly (topical GC)	7/52	Resolution in 3/52

continues

Ref.	Pts	N/R	Organ involved	Study Drug (other drugs)	F'up	Outcome
				Interferon-α		
(106)	44	R	Oral ulcers	IFN-α2a 6-9 million units 3-weekly (PDN 100 mg/day tapering)	30/12	86% responders
(107)	1	N	Oral ulcers	IFN-α $5x10^6$ units im/week (colchicine 1 mg/day)	3 years	Response in 5/52
(108)	12	R	Oral ulcers	IFN-α2a 6 million units day tapered to 3 in 2/12	2/12	9/12 resolved, 2/12 improved
(109)	1	R	Oral ulcers	IFN-α2a 3 million units 3-weekly subsequently increased to 6 million	2/12	Resolved within 10 days
(110)	1	N	Oral ulcers	IFN-α2a 6 million units/day tapering	19/12	Response within 2 weeks
(111)	18	NS	Oral ulcers	IFN-α2a 9 million units 3-weekly tapering for 3/12	1-48/12	6 CR, 9 PR
(112)	18	R	Oral ulcers	IFN-α2a 3 million units thrice weekly increasing to 9 million for a total of 12/52	~12/12	1 CR, 14 PR, 3 treatment failures
(113)	1	N	Oral ulcers	IFN-α 6 million units thrice weekly	ca. 7 years	Oral ulcers resolved within 2/52. IFN discontinued 9/12 later, relapse after ~3 years but response again to IFN-α retreatment
				Infliximab		
(81)	2	NR	Genital ulcers	IFX 3 mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter	13-39	All improved
(87)	1	R	Genital ulcers	IFX 3 mg/kg at 0, 2, 6, then 8-weekly (colchicine, AZA)	NS	Resolved two weeks after the first infusion
(86)	1	R	Genital ulcers	IFX 3 mg/kg at week 0, 2, 6, 12 then 8-weekly (GC, MTX 15 mg/week)	12/12	Response within 2 days
(79)	1	R	Genital ulcers	IFX 5 mg/kg at week 0,2,4,8 (GC)	8	Remission after 2nd infusion
(78)	1	R	Genital ulcers	IFX 5 mg/kg at week 0, 2, 6 then ~8-weekly (PDN 25 mg tapering, MTX)	~94/52	Response
(91)	1	N	Genital ulcers	IFX 5 mg/kg at week 0, 2, 6, 14, 22, then 8-weekly	12/12	Resolved within 8 days
(90)	1	R	Genital ulcers	IFX 5 mg/kg at week 0, 2, 6 (colchicine)	NS	Marked improvement after 1/52, resolved after 3/52
(89)	1	R	Genital ulcers	IFX 10 mg/kg doses 1 month apart (PDN 15 mg/day, MTX 15 mg/week)	13/12	Resolved after the second IFX infusion
(88)	2	R	Genital ulcers	IFX 3-5 mg/kg 2-3 infusions "on demand" (GC)	~2 years	Resolved within a few days
(74)	1	R	Genital ulcers	IFX 3 mg/kg every 8 weeks (MTX 12.5 mg/week)	~ 1 year	Remission
(85)	1	R	Genital ulcers	IFX 5 mg/kg at day 1, 30, then 8-weekly (GC, colchicine)	11/12	Resolution within 10 days
(84)	1	N	Genital ulcers	IFX 3 mg/kg 3 infusion over 4/52 (PDN 60 mg tapering to 10 mg)	1 year	CR
(114)	1	R	Genital ulcers	IFX 5 mg/kg at 0,2,6 15 week	23/52	Resolved after 6/52
(115)	1	R	Genital ulcers	IFX 5 mg/kg at week 0, 2, 6, then 8-weekly (PDN, AZA)	22/12	Marked improvement after the 1st IFX infusion, near-complete healing after the 7th infusion and no relapses thereafter
(94)	7	5R, 2N	Genital ulcers	IFX 5 mg/kg mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter (2 GC, 7 AZA)	32/12	Response noted in 4 out of 7 patients
(95)	1	R	Genital ulcers	IFX 3-5 mg/kg at 0-2-6 weeks then 8-weekly (10 MTX, 8 colchicine, 2 AZA, 5 mesalazine, 2 sulfasalazine, 6 GC)	24/12	Resolved
(96)	2	R	Genital ulcers	IFX 3 mg/kg every 4 weeks then 5 mg/kg every 8 weeks (1 patient) and 3 mg/kg (1 patient) (GC)	up to 21/12	Gradual improvement culminating in remission in one patient and rapid (6 weeks) improvement in the other patients
				Etanercept		
(104)	1	R	Genital ulcers	ETA 25 mg twice weekly (PDN 25 mg/day tapering)	NS	Resolution in 4/52
(101)	1	R	Genital ulcers	ETA 25 mg twice weekly for 3/12 followed by IFX 0,2 and then every 8 weeks (MTX 7.5 mg/week)	1 year	Resolution after the first infusion of IFX
(105)	1	N	Genital ulcers	ETA 25 mg twice weekly (topical GC)	7/52	Resolution in 3/52
				Adalimumab		
(96)	1	R	Genital ulcers	ADA 40 mg eow (GC, AZA, MTX)	~18/12	Partial response with reduced frequency of attacks and of number of ulcers
(97)	2	R	Genital ulcers	ADA (after a course of IFX) (1 GC and MTX)	562 days	One complete and one partial remission
(98)	1	R	Genital ulcers	ADA (after IFX) 40 mg eow (GC)	2/12	Resolution after the first injection
(99)	1	R	Genital ulcers	ADA 80 mg followed by 40 mg eow (GC, colchicine)	60 weeks	Both patients responded to ADA treatment

Ref.	Pts	N/R	Organ involved	Study Drug (other drugs)	F'up	Outcome
				Interferon-α		
(106)	28	R	Genital ulcers	IFN-α2a 6-9 million units 3-weekly (PDN 100 mg/day tapering)	30/12	62% responders
(109)	1	R	Genital ulcers	IFN-α2a 3 million units 3-weekly subsequently increased to 6 million	2/12	Resolved within 10 days
(112)	10	R	Genital ulcers	IFN-α2a 3 million units thrice weekly increasing to 9 million for a total of 12/52	~12/12	3 CR, 5 PR, 2 treatment failures
(111)	13	NS	Genital ulcers	IFN-α2a 9 million units 3-weekly tapering for 3/12	1-48/12	10 CR, 1 PR
(116)	10	N	Genital ulcers	IFN-α2a 3 million units 3-weekly for 1 month tapering (PDN 20 mg/day, SSZ 2 g/day for 3/52, topical GC)	13/12	Resolution within three weeks, remission sustained at 1 year
(108)	11	R	Genital ulcers	IFN-α2a 6x10 million units per day for 2/12	2/12	8/11 resolved, 2/11 improved
(107)	1	N	Genital ulcers	IFN-α $5x10^6$ im/week (colchicine 1 mg/day)	3 years	Response in 5/52
				Infliximab		
(88)	1	R	Papulopustular lesions	IFX 5 mg/kg 2 infusions (GC)	~2 years	Resolved
(92)	1	R	Papulopustular lesions	IFX 5 mg/kg at week 0, 2, 6 then 8-weekly → 3 mg/kg every 3 months (PDN, Cy-A, AZA)	3.5 years	Remission after the 3rd infusion. Cy-A withdrawn and GC tapered off. Follow-up reported in (93)
(87)	1	R	Papulopustular lesions	IFX 3 mg/kg at 0, 2, 6, then 8-weekly (colchicine, AZA)	NS	Resolved two weeks after the first infusion
				Interferon-α		
(111)	10	NS	Papulopustular lesions	IFN-α2a 9 million units 3-weekly tapering for 3/12	1-48/12	4 CR, 4 PR
(109)	1	R	Papulopustular lesions	IFN-α2a 3 million units 3-weekly subsequently increased to 6 million	2/12	Resolved within 10 days
(110)	1	N	Papulopustular lesions	IFN-α2a 6 million units/day tapering	19/12	Response within 2 weeks
(117)	1	N	Papulopustular lesions	IFN-α2a 9 million units 3-weekly for 5/52	8/12	Resolved
				Infliximab		
(92)	1	R	Follicular lesions	IFX 5 mg/kg at week 0, 2, 6 then 8-weekly → 3 mg/kg every 3 months (PDN, Cy-A, AZA)	3.5 years	Remission after the 3rd infusion. Cy-A withdrawn and GC tapered off. Follow-up reported in (93)
(80)	7	R	Follicular lesions	IFX 5-10 mg/kg at 0, 2, 6, 10 (GC and colchicine allowed)	52 days median	Resolved in 2/4 (5 mg/kg) and 1/3 (10 mg/kg)
(83)	7	R	Follicular lesions	IFX 5 or 10 mg/kg at week 0,2,6,10 (GC allowed as rescue treatment)	14/52	Efficacy assessed at 14/52 Resolved in 2/4 cases (5 mg/kg) and 2/3 cases (10 mg/kg) altogether in 4/7 cases
				Etanercept		
(102)	1	R	Follicular lesions	ETA 25 mg twice weekly (PDN final dose 5 mg/kg)	1 year	CR
				Interferon-α		
(106)	31	R	Follicular lesions	IFN-α2a 6-9 million units 3-weekly (PDN 100 mg/day tapering)	30/12	All responded
(108)	6	R	Follicular lesions	IFN-α2a 6x10 million units per day for 2/12	2/12	4/6 resolved, 2 improved
(112)	12	R	Follicular lesions	IFN-α2a 3 million units thrice weekly increasing to 9 million for a total of 12/52	~12/12	1 CR, 6 PR, 5 treatment failures
(107)	1	N	Follicular lesions	IFN-α $5x10^6$ im/week (colchicine 1 mg/day)	3 years	Response in 5/52
(117)	1	N	Follicular lesions	IFN-α2a 9 million units 3-weekly for 5/52	8/12	Resolved
(94)	7	5R, 2N	Follicular lesions	IFX 5 mg/kg mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter (2 GC, 7 AZA)	32/12	Response noted in 3 out of 7 patients
				Infliximab		
(80)	7	R	Erythema nodosum	IFX 5-10 mg/kg at 0, 2, 6, 10 (GC and colchicine allowed)	10	Resolved in 2/4 (5 mg/kg) and 1/3 (10 mg/kg)
(79)	1	R	Erythema nodosum	IFX 5 mg/kg at week 0,2,4,8 (GC)	8	Remission after 2nd infusion
(83)	1	R	Erythema nodosum	IFX 5mg/kg at week 0,2,6,10 (GC allowed as rescue treatment)	14/52	Efficacy assessed at 14/52 Resolved
(94)	7	5R, 2N	Erythema nodosum	IFX 5 mg/kg mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter (2 GC, 7 AZA)	32/12	Response noted in 2 out of 4 patients with erythema nodosum at baseline

continues

Ref.	Pts	N/R	Organ involved	Study Drug (other drugs)	F'up	Outcome
				Etanercept		
(101)	1	R	Erythema nodosum	ETA 25 mg twice weekly for 3/12 followed by IFX 0,2 and then every 8 weeks (MTX 7.5 mg/week)	1 year	Resolution after the first infusion of IFX
				Adalimumab		
(98)	1	R	Erythema nodosum	ADA (after IFX) 40 mg eow (GC)	2/12	Resolution after the first injection
				Interferon-α		
(113)	1	N	Erythema nodosum	IFN-α 6 million units thrice weekly	ca. 7 years	Resolved within 1/12
(111)	7	NS	Erythema nodosum	IFN-α2a 9 million units 3-weekly tapering for 3/12	1-48/12	3 CR, 2 PR
(106)	26	R	Erythema nodosum	IFN-α2a 6-9 million units 3-weekly (PDN 100 mg/day tapering)	30/12	All responded
(112)	8	R	Erythema nodosum	IFN-α2a 3 million units thrice weekly increasing to 9 million for a total of 12/52	~12/12	2 CR, 5 PR, 1 active
(108)	6	R	Erythema nodosum	IFN-α2a 6x10 million units per day for 2/12	2/12	4/6 resolved, 1/6 improved
(107)	1	N	Erythema nodosum	IFN-α $5x10^6$ im/week (colchicine 1 mg/day)	3 years	Response in 5/52
			Ocular Behçet			
				Infliximab		
(118)	1	R	Anterior uveitis	IFX 5 mg/kg 0, 2, 6, then 8 weekly (PDN 10 mg, AZA 150 mg)	~2 years	Resolved
(74)	1	R	Posterior uveitis	IFX 5 mg/kg every 8 weeks (MTX 10 mg/week)	NS	Improvement within days
(119)	13	R	Posterior uveitis	IFX 5 mg/kg at week 0, 2, 6, 14 (GC, AZA)	54/52	4 complete, the remaining partial response
(120)	2	R	Posterior uveitis	IFX 5 mg/kg at week 0,2,6 than 8-wkly	31-54/12	Both responded
(121)	12	R	Posterior uveitis	IFX 5 mg/kg 9 infusions over 1 year (PDN 1 mg/kg/day tapering)	≤6/12	CR in 9/12 (75%) at 12 months, at 24 months 7/9 (78%) still in remission
(122)	6	R	Posterior uveitis	IFX 3 mg/kg 1-12 infusions	≥2 years	All responders – VA improved or stable in 5/6
(80)	13	R	Posterior uveitis	IFX 5-10 mg/kg at 0, 2, 6, 10 week (7 for 5 mg and 6 for 10 mg) (GC and colchicine allowed)	10	Ocular attacks resolved in 5/7 (5 mg/kg) and 5/6 (10 mg/kg) patients, VA improved in 5/7 and 4/6 eyes
(93)	1	R	Posterior uveitis	IFX 5 mg/kg at weeks 0, 2, and 6 and subsequently every 2 months for a total of 13 infusions	2 years	Remission after the 3rd infusion
(123)	5	R	Posterior uveitis	IFX 5 mg/kg at week 0, 2, 6	3 years	All improved after first dose, additional doses required in 4/5
(124)	3	R	Posterior uveitis	IFX 5 mg/kg at 0, 2, 6 weeks (GC, MTX)	≥6/52	(1) macular oedema resolved in 1/52, (1) response in 2-12 weeks, (1) response at 1 week
(125)	6	R	Posterior uveitis	IFX 5 mg/kg at week 0,2,6 than 8-weekly (GC/various immunosuppressants)	23/12	6/6 in remission by 2/12, 3/6 attack-free in the follow-up, GC and immunosuppressants tapered
(126)	1	R	Posterior uveitis	IFX 5 mg/kg three infusions within 42 days	30/12	Remission after the second infusion
(127)	7	R	Posterior uveitis	IFX 3-5 mg/kg at week 0,2,4,8 than 6-8 weekly	23/12	Relapse frequency reduced to 1/3 of pretreatment, VA better in 4 stable in 9 eyes
(128)	4	R	Posterior uveitis	IFX 5 mg/kg at 0,15,45 days	mean 11 months	2/4 responders (assessed 2/52 after the last infusion of IFX) with transient benefit
(129)	12	R	Posterior uveitis	IFX 5 mg/kg at 0, 14 days, monthly for 4-6/12, then pro re nata (10 patients were on PDN, 6 patients were on MTX or AZA)	16.7±8/12	11/12 (91.6%) responded with reduced frequency of relapses, PDN dose tapered from 24 to 9 mg/day. VA improved in 12.5% eyes and was unchanged in 87.5% of eyes
(130)	1	R	Posterior uveitis	IFX 5 mg/kg at week 0, 2, 6 then 8 weekly later switched to 6-weekly (GC, AZA)	~46 weeks	Remission after the 2nd infusion, minor relapse on 8-weekly infusion regimen (resolved switching to 6-weekly)
(131)	4	R	Posterior uveitis	IFX 5 mg/kg 0-2-6 then 8-weekly (GC, immunosuppressants)	7-22 months	Effective in all cases
(132)	5	R	Posterior uveitis	IFX 5 mg/kg single infusion (PDN 50 mg/day, range 20-80 mg).	mean 9.8/12	All responded within 4 weeks, most patients relapsed after discontinuation of IFX
(133)	3	1N, 2R	Posterior uveitis	IFX 5 mg/kg single infusion (n=2) and 3 mg/kg at 0, 2, 4 and 6 weeks (PDN 0, 20, and 60 mg plus cyclosporine)	3 weels	All improved, one patient had a full remission

Ref.	Pts	N/R	Organ involved	Study Drug (other drugs)	F'up	Outcome
(115)	1	R	Posterior uveitis	IFX 5 mg/kg at week 0, 2, 6, then 8-weekly (PDN, AZA)	22/12	Marked vision improvement after the 1st IFX infusion, relapse-free course
(22)	17	R	Posterior uveitis	IFX 5 – 10 mg/kg at week 0, 2, 6, then 8-weekly	6/12	The number of uveitis attacks decreased from 3.1±2.7 (mean±SD) in the pretreatment period to 0.4±1.0 after onset of IFX therapy; 82% of patients remained relapse-free.
(94)	7	5R, 2N	Posterior uveitis	IFX 5 mg/kg mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter (2 GC, 7 AZA)	32/12	Response noted in 3 out of 7 patients
(134)	1	R	Posterior uveitis	IFX 5 mg/kg t week 0,2,4,8 than 6 weekly	4 years	Remission
(98)	1	R	Posterior uveitis	IFX 5 mg/kg t week 0,2,4,8 than 5-8 weekly (GC, Cy-A)	6/12	Response of uveitis, but the patient developed neuro-Behçet
(135)	11	R	Posterior uveitis	IFX (regimen not specified) (9 colchicine, 6 PDN and 7 Cy-A tapering)	18-50/12	2 patients entered complete remission, all patients had a favourable response, in 3 the frequency of ocular attacks increased after 12 months of IFX therapy
(136)	4	R	Posterior uveitis	IFX 5 mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter (PDN 5-10 mg/day, 3 AZA, 3 Cy-A)	~28/12	Complete remission, 2 patients relapsed after IFX was stopped
(137)	13	R	Posterior uveitis	IFX 5 mg/kg at week 0, 2, and 6 weeks and then every 8 weeks (PDN <10 mg/day)	54/52	11 patients remission, 1 partial remission, 1 no response
(138)	1	R	Posterior uveitis	IFX 5 mg/kg at week 0, 2, and 6 weeks and then every 8 weeks (Cy-A)	1 year	Remission, but IFX had to be stopped due to the development of anaphylaxis (successfully replaced by ADA)
(139)	53	R	Posterior uveitis	IFNα2a 4.5,000,000 IU3 per week for the first 3 months followed by 3,000,000 IU 3 times per week for the next 3 months (GC)	12-130/12	84.9% of patients responded to treatment
(81)	10	NR	(Posterior) uveitis	IFX 3 mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter	13-39	All improved
(140)	1	R	Panuveitis	IFX 5 mg/kg at week 0, 2, 6 (PDN 1 mg/kg tapering, MTX)	26/52	Major response sustained for 5/12 after last infusion
(131)	4	R	Panuveitis	IFX 5 mg/kg at week 0, 2, 6, then 8-weekly (PDN, in 3/4 MTX added later)	7-22/12	All patients responded, one patient had a transient attack of anterior uveitis
(141)	5	R	Panuveitis	IFX 5 mg/kg single infusion (1 patient PDN and Cy-A, 1 Cy-A, 1 Cy-A and AZA)	28 days	CR within a week
(142)	3	R	Panuveitis	IFX 5 mg/kg at week 0, 2, 6, 14, 18, 26 then as required; subsequently switched to ADA in all (all GC + IS = 1 MTX, 1 AZA, 1 mycophenolate)	~3 years	All responded, in 2 cases IFX withdrawal caused a flare but IFX reintroduction brought again the disease under control, no flare under ADA treatment
(85)	2	R	Panuveitis	IFX 5 mg/kg at day 1, 30, then 8-weekly (1 GC and colchicine, 1 GC, AZA and colchicine)	11-16/12	Resolution within 7-10 days
(143)	1	R	Panuveitis	IFX 5 mg/kg 3 infusions in 6 weeks (MTX 25 mg/week, PDN 60 mg tapered to 6 mg daily)	18/12	Marked improvement after the 3rd IFX infusion and no further relapses
(13)	1	R	Panuveitis/posterior uveitis with retinal vasculitis	IFX 5 mg/kg at week 0, 2, 6, 7 then 8-weekly (PDN 25 mg/daily)	13/12	Relapse after 13 months of IFX treatment
(144)	23	R	Panuveitis/posterior uveitis with retinal vasculitis	IFX 5 mg/kg (1 patient 10 mg/kg) at week 0, 2, 6, then 8-weekly (2 colchicine, 6 PDN 10 mg/day tapering, 2 Cy-A)	≥6/12	10 patients were disease-free, 13 had recurrent uveitis
(89)	1	R	Retinal vasculitis	IFX 10 mg/kg doses 1 month apart (PDN 15 mg/day, MTX 15 mg/week)	13/12	Resolved after the second IFX infusion
(145)	1	R	Retinal vasculitis	IFX 3 mg/kg at week 0, 2, 6	22/52	Near-complete response after the second infusion, IFX stopped after the third infusion because of pyomyositis
(91)	1	N	Retinal vasculitis	IFX 5 mg/kg at week 0, 2, 6, 14, 22, then 8-weekly	12/12	Resolved within 8 days
(137)	13	R	Retinal vasculitis	IFX 5 mg/kg at week 0, 2, and 6 weeks and then every 8 weeks (PDN <10 mg/day)	54/52	10 patients remission, 2 partial remission, 1 no response
(146)	1	R	Posterior uveitis and retinal vasculitis	IFX 2.5-10 mg/kg 43 infusions over 5 years	5 years	Remission after receiving IFX regularly (5 mg/kg every 4/52)

continues

Ref.	Pts	N/R	Organ involved	Study Drug (other drugs)	F'up	Outcome
(147)	25	R	Posterior uveitis and retinal vasculitis	IFX 5 mg/kg 0, 4, 8, 16, 24 (6 patients on GC alone, 3 on IS alone, 16 on GC + IS)	~32 weeks	All patients received one IFX infusion. Response by day 28: retinitis-vitritis CR 100%, retinal vasculitis 94%, CME 90%. 15 patients received four further infusions. CR was attained in 60%.
(148)	10	R	Posterior uveitis and retinal vasculitis	IFX 5 mg/kg at week 0 and 2, then if required 8-weekly to 6-weekly (GC, 2 AZA, 8 Cy-A)	3 years	Patients had posterior uveitis (=10), retinal vasculitis (6). Three pts remitted after 2 infusions. There was a significant reduction in the frequency of ocular attacks. Retinal vasculitis remitted in all patients
(79)	1	R	Posterior uveitis and retinal vasculitis	IFX 5 mg/kg at week 0,2,4,8 (GC)	8	Remission after 2nd infusion
(149)	10	R	Posterior uveitis and retinal vasculitis	IFX 5 mg/kg at 0 and at 2, 4, 6, 8, and 10 weeks (PDN 0.25 mg/kg/day to 0.5 mg/kg/day, AZA)	30/12	Compared to patients treated with GC + IS, in the IFX group relapses were 1.2/2 years vs 6.3 years
(83)	13	R	Posterior uveitis and retinal vasculitis	IFX 5 or 10 mg/kg at week 0,2,6,10 (GC allowed as rescue treatment)	14/52	Efficacy assessed at 14/52 Ocular attacks resolved in 5/7 cases (5 mg/kg) and 5/6 cases (10 mg/kg) altogether in 10/13 cases. VA improved in 5/7 and 4/6 cases.
(78)	1	R	Posterior uveitis and retinal vasculitis	IFX 5 mg/kg at week 0, 2, 6 then ~8-weekly (PDN 25 mg tapering, MTX)	~94/52	Response
(150)	14	R	Posterior uveitis and retinal vasculitis	IFX 5 mg/kg at week 0, 2, 6 then 8-weekly (1 MTX, 4 GC, 12 Cy-A tapered in 9)	19/12	At 12 months, 8/14 patients (57%) had experienced no flares. Visual acuity improved or remained unchanged at 12 months in 26/28 eyes (93%)
(151)	1	R	Retinal vasculitis	IFX 5 mg/kg every 6 weeks, than 8-weekly (PDN 15 mg increased to 60 mg daily, AZA, colchicine)	~3 years	Rapid clinical response and normalisation of retinal angiography findings
(92)	1	R	CME	IFX 5 mg/kg at week 0, 2, 6 then 8-weekly → 3 mg/kg every 3 months (PDN, Cy-A, AZA)	3.5 years	Response after 3rd infusion, CR after 6/12. Cy-A withdrawn and GC tapered off. Follow-up reported in (93)
(152)	1	R	Retinal neoangiogenesis and posterior uveitis	IFX	12/12	Ocular inflammation subsided nearly completely; regression of retinal neovascularisation within 8 months
(153)	1	R	Scleritis	IFX 5 mg/kg 3 doses (GC, MTX, colchicine)	6/52	VA worsened at week 6, developed erythema nodosum
(118)	1	R	Scleromalacia perforans	IFX 5 mg/kg 0, 2, 6, then 8 weekly (PDN 10 mg, AZA 150 mg)	~2 years	Treatment failure (required surgery)
(154)	1	R	Vitritis and CME	IFX three infusions (regimen NS) (PDN 20-30 mg/day)	NS	Not effective
(154)	1	R	Vitritis, iritis, rubeosis iridis	IFX three infusions (regimen NS)	NS	Response to 1st IFX infusion, relapses 1 year after 1st infusion and 3/12 after 2nd infusion
				Adalimumab		
(155)	11	R	(Posterior) uveitis	ADA 40 mg eow (7 PDN ≥15 mg/day, 9 colchicine, 2 AZA, 2 Cy-A, 1 MTX)	4-17/12	10/11 responded to ADA therapy
(97)	2	R	(Posterior) uveitis	ADA (after a course of IFX) (GC, 1 MTX)	562 days	Partial response
(13)	1	R	Panuveitis/posterior uveitis with retinal vasculitis	ADA 40 mg every other week (GC, cyclosporine)	18/12	Remission after 10 weeks of ADA treatment
				Etanercept		
(102)	1	R	Posterior uveitis and retinal vasculitis	ETA 25 mg twice weekly (PDN final dose 5 mg/kg)	1 year	Remission within 2/12
(102)	1	R	Retinal vasculitis	ETA 25 mg twice weekly (PDN final dose 5 mg/kg)	1 year	Responded
				Interferon-α		
(156)	37	R	Panuveitis	IFN-α2a 3,000,000 IU/day tapering to thrice weekly in the absence of flares, otherwise adjusted as required (17 patients received GC)	24/12	95% of patients responded, in 41% the dose of IFN-α2a could be tapered according to the protocol without flares

Ref.	Pts	N/R	Organ involved	Study Drug (other drugs)	F'up	Outcome
(157)	44	R	Posterior uveitis	IFN-α2a 3-6 million units day tapering (GC <10 mg/day allowed)	6/12	16 responded, remained relapse-free 24 responded but had still recurrent uveitis 4 treatment failures
(158)	8	R	Posterior uveitis	IFN-α 3 million units 3-weekly (GC)	22/12	All responders, PDN dose tapered from 47 to 8.5 mg/day
(108)	3	R	Posterior uveitis	IFN-α2a 6x10 million units per day for 2/12	2/12	All responders
(159)	50	2N, 48R	Posterior uveitis or panuveitis	IFN-α2a 6x10 million units day tapering (PDN ≤10 mg/day)	36.4/12	92% responders - remission of retinal inflammation by week 24
(160)	23	R	Posterior or panuveitis	IFN-α2a 3 million units 3-weekly (PDN 1 mg/kg/day tapering)	mean 29.6 months	82.6% responders. IFN discontinued in 10 (22.2%), 4 relapses upon treatment discontinuation
(161)	32	R	Posterior uveitis or panuveitis	IFN-α2a 3 million units 3-weekly (PDN 1 mg/kg tapering)	mean 70.6 months	88% responded, IFN discontinued in 68% of patients after 32/12 of treatment
(162)	10	R1, N9	Posterior uveitis and retinal vasculitis	IFN-α2b 5 million units thrice weekly (AZA 2.5 mg/kg/day) for 24/52	≥24/52	VA improved, four patients had transient flares during treatment
(163)	1	R	Panuveitis and retinal vasculitis	IFN-α2b 3 million units 3-weekly (PDN 100 mg/day tapering)	2 years	Suppression of inflammation, PDN dose tapered to 10 mg/day
(164)	50	R	Panuveitis/posterior uveitis with retinal vasculitis	IFN-α2a 6 million units daily tapering according to the clinical response (PDN ≤10 mg/day)	29.5 months mean	92% of patients responded to treatment, 17 patients weaned off treatment without relapse
(110)	1	N	Retinal vasculitis	IFN-α2a 6 million units/day tapering	19/12	Response within 2 weeks
(165)	1	R	Retinal vasculitis	IFN-α2a 9 million units 3-weekly (PDN 100 mg/day tapering)	4 years	Resolution within 2 weeks sustained at 4 years, PDN stopped
(166)	1	R	Retinal vasculitis	IFN-α 3 million units 3-weekly for 2 years then tapering (colchicine, low-dose PDN)	>2 years	Improved
(167)	3	R	Retinal vasculitis	IFN-α2b 3 million units thrice weekly (1 CYC, 1 colchicine and GC, 1 cyclosporine and colchicine)	Up to 3 years	CR
(168)	1	R	Retinal vasculitis	IFN-α2a 6 million units tapering	52 days	Retinal vasculitis and optic disk neovascularisation resolved within 7/52
(117)	1	N	Retinal vasculitis and iridocyclitis	IFN-α2a 9 million units 3-weekly for 5/52 (colchicine)	8/12	Resolved in 2/52
(169)	7	N+R	Optic disk neovascularisation	IFNα-2a 6 million units per day tapering	median 24/12	All treated patients responded
				Rituximab		
(170)	1	R	Retinal vasculitis	RTX 1000 mg 2 infusions two weeks apart	24/12	Improvement in vasculitis and VA (8/10) within 6 weeks
			Arthritis			
				Infliximab		
(127)	7	R	Arthritis	IFX 3-5 mg/kg at week 0,2,4,8 than 6-8 weekly	23/12	Resolved
(91)	1	N	Arthritis	IFX 5 mg/kg at week 0, 2, 6, 14, 22, then 8-weekly	12/12	Resolved within 8 days
(87)	1	R	Arthritis	IFX 3 mg/kg at 0, 2, 6, then 8-weekly (colchicine, AZA)	NS	Improvement two weeks after the first infusion but left total knee replacement required
(85)	1	R	Arthritis	IFX 5 mg/kg at day 1, 30, then 8-weekly (GC, colchicine)	11/12	Resolution within 10 days
(81)	10	NR	Arthritis	IFX 3 mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter	13-39	All improved
(79)	1	R	Arthritis	IFX 5 mg/kg at week 0,2,4,8 (GC)	8	Remission after 2nd infusion
(88)	2	R	Arthritis	IFX 3-5 mg/kg 2-3 infusions "on demand" (GC)	~2 years	Resolved, a patient had 2 relapses but responded again to IFX
(95)	10	R	Arthritis	IFX 3-5 mg/kg at 0-2-6 weeks then 8-weekly (10 MTX, 8 colchicine, 2 AZA, 5 mesalazine, 2 sulfasalazine, 6 GC)	24/12	Patients had concomitant intestinal manifestations of ABD. Arthritis resolved in all patients
				Etanercept		
(104)	1	R	Arthritis	ETA 25 mg twice weekly (PDN 25 mg/day tapering)	NS	Improved after 4/52

continues

Ref.	Pts	N/R	Organ involved	Study Drug (other drugs)	F'up	Outcome
				Interferon-α		
(106)	39	R	Arthritis	IFN-α2a 6-9 million units 3-weekly (PDN 100 mg/day tapering)	30/12	38 patients responded
			Neuro-Behçet			
				Infliximab		
(171)	1	R	Neuro-Behçet	IFX 5 mg/kg at week 0, 2, 6 then 8-weekly (pulse GC at onset, MTX 10 mg/week)	NS	CR within 1 week
(172)	1	R	Neuro-Behçet	IFX 5 mg/kg at week 0, 2, 6	1 month	Clinical and MRI resolution after the second IFX infusion
(173)	8	R	Neuro-Behçet	IFX 5 mg/kg at week 0, 2, 6 (GC, 2 MTX and 1 cyclosporine)	~1-3 years	All improved, no progression of MRI lesions, IFX safely withdrawn in 1 patient and switched to ETA in another
(120)	1	R	Neuro-Behçet	IFX 5 mg/kg at week 0,2,6 than 8-weekly	54/12	Response
(174)	1	R	Neuro-Behçet	IFX 3 mg/kg at week 0,2,6 (MP, CYC and MTX)	6 weeks	Clinical and MRI improvement after 2nd infusion
(175)	5	R	Neuro-Behçet	IFX 5 mg/kg at 0, 2, 6, and 14 weeks (MTX, PDB <10 mg/day)	24 weeks	By week 24, 3/5 had improved, none worsened by clinical and MRI criteria
(176)	1	R	Neuro-Behçet	IFX 5 mg/kg at 0,2,6 weekly than bimonthly for 1 year (colchicine, GC; CYC for 6/12, then AZA)	21 months	Clinical and MRI response, relapse 7/12 after stopping IFX, again response to IFX retreatment
(177)	1	R	Neuro-Behçet	IFX 3 mg/kg at week 0-2-4 and 8 → AZA + GC → ADA 40 mg every other week	2 years	Response, in remission for 1 year after IFX. After relapsing on GC and AZA treated with ADA with marked improvement after 3/12 and no relapse afterwards.
(178)	1	R	Neuro-Behçet	IFX 3 mg/kg at 0, 2, 6, 12, 24 weeks (GC, colchicine)	24/52	"Dramatic" response followed by loss of efficacy
(179)	1	R	Neuro-Behçet	IFX 3 mg/kg (MTX) → ETA 25 mg twice weekly	3 years ~1 year	Clinical response to IFX, only 2 relapses in 3 years ETA effective, GC withdrawn
(84)	1	N	Neuro-Behçet	IFX 3 mg/kg at weeks 0, 2 and 6 (PDN 60 mg tapering to 10 mg)	1 year	Clinical and MRI remission
(127)	7	R	Neuro-Behçet	IFX 3-5 mg/kg at week 0,2,4,8 than 6-8 weekly	23/12	Responded
(134)	1	R	Neuro-Behçet	IFX 5 mg/kg t week 0,2,4,8 than 6 weekly	4 years	Remission
(180)	4	1N, 3R	Neuro-Behçet	IFX 3 (2 patients) and 5 (2 patients) mg/kg (GC, colchicine and CYC in 3 patients)	3 years	No progression in 2 patients (treated with IFX 5 mg/kg), progressive course in 2 patients (treated with IFX 3 mg/kg)
(181)	1	R	Neuro-Behçet	IFX 5 mg/kg at 0, 2, 6, weeks than 8-weekly (MTX 15 mg/weekly)	27/12	Resolution of acute neurological attacks, some residual neurological features
(137)	5	R	Neuro-Behçet	IFX 5 mg/kg at week 0, 2, and 6 weeks and then every 8 weeks (PDN <10 mg/day)	54/52	Remission
(143)	1	R	Neuro-Behçet	IFX 5 mg/kg 3 infusions in 6 weeks (MTX 25 mg/week, PDN 60 mg tapered to 6 mg daily)	18/12	Marked clinical improvement and resolution of CNS MRI lesions after the 3rd IFX infusion; no further relapses at follow-up
				Adalimumab		
(97)	2	R	Neuro-Behçet	ADA (after a course of IFX) (2 GC, 1 cyclosporine, 1 AZA)	562 days	Complete response
(98)	1	R	Neuro-Behçet	ADA (after IFX) 40 mg eow (GC)	2/12	Clinical improvement and resolution of active MRI brain lesions
				Interferon-α		
(113)	1	N	Neuro-Behçet	IFN-α 6 million units thrice weekly	ca. 7 years	Seizures resolved within 5/12. IFN discontinued 4/12 later, relapse after ca. 3 years but response again to IFN-α
(117)	1	N	Neuro-Behçet	IFN-α2a 9 million units 3-weekly for 5/52	8/12	Clinical and MRI features resolved in 3/52
			Vasculo-Behçet			
				Infliximab		
(182)	1	R	Arterial aneurysms in MAGIC syndrome	IFX 3 → 5 mg/kg 4- then 8-weekly (intravenous GC, then PDN 10 mg/day)	2 years	Aneurysm stabilisation
(183)	1	N	Pulmonary artery aneurysms with thrombi	IFX 5 mg/kg for 14 months (regimen NS)	>2 years	Resolution of thrombi within 2/52 and marked reduction of pulmonary artery aneurysms within 6/12

Ref.	Pts	N/R	Organ involved	Study Drug (other drugs)	F'up	Outcome
(184)	1	N	Pulmonary artery aneurysms with thrombi	IFX 5 mg/kg at weeks 0, 2, 6, 14, and 22 (GC, AZA)	15/12	Resolution of thrombi and marked reduction of pulmonary artery aneurysms observed 6/12 after therapy onset
			Venous involvement			
				Infliximab		
(88)	1	R	Superficial thrombophlebitis	IFX 3 mg/kg 2 infusions (GC)	~2 years	Responded
(79)	1	R	Thrombophlebitis	IFX 5 mg/kg at week 0,2,4,8 (GC)	8	Remission after 2nd infusion
(127)	7	R	Thrombophlebitis	IFX 3-5 mg/kg at week 0,2,4,8 than 6-8 weekly	23/12	Resolved
(185)	3	R	Deep venous thrombosis (Budd-Chiari)	IFX 3 mg/kg (1 g MP)	3/52	2 patients had liver failure at onset of IFX treatment and died. All patients were treatment failures
				Adalimumab		
(186)	1	R	Pulmonary artery aneurysms with thrombi	ADA 40 mg eow for 8 weeks (PDN initial dose not stated tapered to 2.5 mg/day)	2 months	Reduction of pulmonary artery aneurysm size
				Interferon-α		
(108)	1	R	Thrombophlebitis	IFN-α2a 6x10 million units per day for 2/12	2/12	Resolved
			GE Behçet			
				Infliximab		
(88)	2	R	GE Behçet	IFX 3-5 mg/kg 2-3 infusions "on demand" (GC)	~2 years	Resolved (1 relapsed, but responded to IFX retreatment)
(81)	10	NR	GE Behçet	IFX 3 mg/kg at week 0, 2, and 6 weeks and every 8 weeks thereafter	13-39	Ileocecal ulcers improved in all after 2 weeks and resolved in 9/10 by 12 months
(153)	1	NS	GE Behçet	IFX 5 mg/kg 4 doses	~14/52	Rectal discharge not improved, developed erythema nodosum
(187)	1	N	GE Behçet	IFX 5 mg/kg at day 1, 13, and 42 after surgery for esophageal perforation (AZA 50 mg/day increasing to 100 mg/day)	NS	Resolution of esophageal ulcer
(188)	1	R	GE Behçet	IFX 5 mg/kg 1 infusion (MP 40 mg/day, AZA, mesalamine, colchicine)	15 days	Pain a resolved almost entirely in 2/52, colonoscopy performed later showed resolution of the gut ulcers
(189)	1	R	GE Behçet	IFX 5 mg/kg at 0, 2, 7, 23 weeks (PDN 7.5 mg/day)	23/52	Near-complete remission at 9 weeks, PDN discontinued
(190)	4	R	GE Behçet	IFX 5 mg/kg at 0-2-6 weeks then 8-weekly	26 days-3 years	Remission in 4/6 patients, 2 required surgery
(191)	1	R	GE Behçet	IFX 5 mg day 0 and after 1 month	12 months	Abdominal pain resolved 5/12 after starting IFX, asymptomatic after 1 year
(192)	1	R	GE Behçet	IFX 300 mg infusion (GC)	1 week	Intestinal ulcer healed in 1/52
(193)	1	N	GE Behçet	IFX 5 mg/kg 3 infusions over 6 weeks (GC, AZA)	~9/12	Resolution of intestinal ulcers after 2nd IFX infusion
(95)	10	R	GE Behçet	IFX 3-5 mg/kg at 0-2-6 weeks then 8-weekly (10 MTX, 8 colchicine, 2 AZA, 5 mesalazine, 2 sulfasalazine, 6 GC)	24/12 at 12 months	Iliocecal ulcers resolved in 9 of 10 patients
				Adalimumab		
(97)	3	R	GE Behçet	ADA (after a course of IFX) (GC and various immunosuppressants)	562 days	1 complete and 2 partial responses
(99)	2	R	GE Behçet	ADA 1 patient 160 mg followed by 80 mg and then 40 mg eow, 1 patient 80 mg followed by 40 mg eow (GC, colchicine)	60 weeks	Both patients responded to ADA treatment
				Interferon-α		
(110)	1	N	GE Behçet	IFN-α2a 6 million units/day tapering	19/12	Resolution of colonscopy lesions after 4 months
(113)	1	N	GE Behçet	IFN-α 6 million units thrice weekly tapering after clinical response	ca. 3 years	Resolved within 9/52

N/R (New/refractory): "refractory" means patients with insufficient or no response to treatment with glucocorticoids and/or at least 1 immunosuppressant, "new (treatment)" means patients who have not previously been treated or who have previously been successfully treated, but in whom treatment was withdrawn for reasons other than lack of efficacy prior to receiving biological agents. For a full list of the abbreviations used in this Table, please refer to "List of abbreviations used in this paper and in the Tables (in alphabetical order)" in the main text.

patients with refractory mucocutaneous disease, 89% of those with ocular disease, 100% of those with gastrointestinal disease, and 91% of those with central nervous system involvement. Combination of infliximab with azathioprine, cyclosporine, or both, appeared to be superior to monotherapy for sustained ocular remission. Most patients (n=325) received IFX, 37 received ETA, and 28 ADA.

– Switch between TNF-α inhibitors in Adamantiades-Behçet's disease

Although IFX remains the most used TNF-α inhibitor in ABD, lack or loss of efficacy and infusion reactions may limit its use. A review of 69 patients treated with IFX for ABD revealed that 17 (25%) were switched to ADA because of inefficacy (n=15) or infusion reactions (n=2) (13). In 10 out of these 17 patients, the main manifestations requiring switching were mucocutaneous lesions, in 4 retinal vasculitis, and in 3 neurological involvement. Of those patients switched to ADA, nine entered sustained remission and three had a favourable response to treatment. One patients with retinal vasculitis and two patients with neurological involvement (all resistant to IFX therapy) did not respond to ADA. ADA was well tolerated in all patients. These data suggest that switching from a TNF-α inhibitor to another may be justified in patients with ABD who show lack or loss of efficacy or develop drug-specific reactions to a particular TNF-α inhibitor.

– Uncontrolled studies on interferon-α (not reported in Table I)

In a study on 14 untreated ABD patients with a variety of clinical manifestations, IFN-α2a (3 million units thrice weekly for ~2 months) significantly decreased the frequency and increased remission duration of orogenital ulcers and pustular lesions with a non-significant trend for improvement of erythema nodosum and thrombophlebitis (14).

In a 48-week open-label trial on 20 untreated ABD patients, IFN-α2b at 5 million units thrice weekly for six weeks followed by the same dose once weekly for further ten weeks significantly reduced the mean number and duration of arthritis attacks with some but non-significant improvement in mucocutaneous lesions (15). None of the above studies specified how many patients with a given clinical manifestations improved following biological treatment.

A retrospective study reported on the outcomes of 53 patients with severe posterior uveitis related to ABD treated with IFN-α2a at an initial dosage of 6 million IU per day tapering (16). IFN was discontinued in patients with quiescent ocular inflammation, bu resumed in case of relapses. Patients were followed up for 2 years or longer. Of 53 patients, 52 (98.1%) responded to IFN. In 47 patients (88.7%), IFN could be discontinued when the disease was in remission. Twenty of these 47 (42.6%) needed a second treatment course during a median followup of 6.0 years. Visual acuity improved or remained unchanged in 91 eyes (94.8%). Ocular disease was still in remission in 50% of the patients 45.9 months after cessation of the first IFN course. These findings indicate that IFN has a favourable effect on the prognosis of ocular inflammation and that it can also induce longlasting remissions in patients with ocular manifestations of ABD.

A review of studies performed using IFN-α in ABD concluded that efficacy of such treatment could be demonstrated in 94% of patients with inflammatory ocular disease, in 95% of those with articular manifestations, and in 86% of those with mucocutaneous manifestations (17).

– Uncontrolled studies on tocilizumab

The interleukin-6 (IL-6) receptor (IL-6R) antagonist tocilizumab has successfully been used to treat a patient with refractory neuro-Behçet (18). The rationale for using tocilizumab in neuro-Behçet is the evidence of raised IL-6 concentrations in the cerebrospinal fluid of patients with active neuro-Behçet (19). Raised IL-6 levels have also been reported in the sera from patients with active ABD compared to controls (20) including those with ocular disease due to ABD compared with patients with inactive ocular disease and controls (21). This data suggests that IL-6 may be involved in the pathogenesis of ABD and thus a role for tocilizumab as treatment for ABD.

Studies comparing synthetic disease-modifying anti-rheumatic drugs with biological agents in Adamantiades-Behçet's disease

– Interferon-α

There is an ongoing RCT, Interferon-alpha2a Versus Cyclosporin A for Severe Ocular Behçet's Disease (INCYTOB; ClinicalTrials.gov Identifier: NCT00167583, http://clinicaltrials.gov/ct2/show/NCT00167583) comparing the efficacy and safery of cyclosporine (3 mg/kg bw, augmented to 5 mg if necessary and combined with prednisolone) and of IFN-α2a (3-6 million IU per day subcutaneously, augmented to up to 9 if necessary and later reduced according to clinical response to 3 x 3 million IU /week). The results of this trial are not yet available.

– Infliximab

A retrospective review of thirty-seven ABD patients with uveitis documented the respective efficacy and safety profiles of cyclosporine and IFX (22). Twenty patients received cyclosporine (3–5 mg/kg/day) and 17 patients were treated with IFX (5–10 mg/kg) at week 0, 2, 6 and 8-weekly thereafter. The majority of patients in this study had received prior treatment, with the cyclosporine patient group previously being given colchicine with or without systemic glucocorticoids and the IFX group beng given cyclosporine with or without systemic glucocorticoids. These previous treatments were converted to either cyclosporine or IFX due to the side effects or because of a poor response to the original therapy. Comparing the 6-month pretreatment with the 6-month post-treatment period, the number of uveitis attacks decreased from 3.3±2.4 to 1.2±1.2 (mean±SD) in the cyclosporine group and from 3.1±2.7 to 0.4±1.0 in the IFX group. In addition, the number of uveitis attacks during the 6 months after the initiation of the treatments was significantly less in the IFX group as compared to the cyclosporine group. Out of the 20 patients treated with cyclosporine, nine patients

(45%) had no acute episodes of uveitis during the 6 months of therapy, while in the IFX group 14 out of 17 (82%) remained relapse-free. All these between-group differences were statistically significant. In contrast, there was no significant difference in terms of VA improvement in the two study groups, possibly because of irreversible ocular changes that could not be reversed by treatment. No serious adverse events were observed in either group. In the cyclosporine group, only one patient had neurological symptoms and renal toxicity that required a dose reduction, while in the IFX group leucopenia and an infusion reaction were seen in one patient each. These results may suggest that IFX could be superior to cyclosporine in preventing ocular inflammation in ABD.

Published guidance on the use of biological agents in Adamantiades-Behçet's disease

Recommendations on the use of biological agents to treat ABD have been published by the EULAR in 2008 (23). Overall, our recommendations are consonant with those endorsed by the EULAR in advising using biological agents in refractory cases only. Refractory manifestations that may warrant biological treatment according to the recommendations by the EULAR include severe eye, CNS, gastrointestinal, joint, and mucocutaneous involvement. However, according to the EULAR recommendations, biological agents may also be used as first-line therapy in cases of severe eye disease, defined as greater than 2 lines of drop in visual acuity on a 10/10 scale; retinal vasculitis; and macular involvement. In these scenarios, IFX (or cyclosporine) may be used in combination with GC and AZA; alternatively, IFN-α (with or without GC) may also be used.

On the basis of the literature available, we formulate the following recommendations:

- Biological (TNF-α inhibiting and interferon-α [IFN-α]) agents can not be recommended as monotherapy (*i.e.* without glucocorticoids) for ABD because of lack of evidence.
- Biological (TNF-α inhibiting and IFN-α) agents can not be recommended as first-line, add-on therapy to glucocorticoids or other medications of recognised efficacy in newly diagnosed ABD because of lack of, or very limited evidence. An exception is sight-threatening ocular inflammation (level of evidence 5, strength of recommendation D, see below).
- In patients with parenchymal central nervous system involvement (clinical neurological manifestations with evidence of active MRI lesions consistent with ABD) refractory to glucocorticoids given at adequate doses (1 mg/kg/die of prednisone-equivalent with or without methylprednisolone pulses with subsequent gradual tapering), immunosuppressive agents (such as cyclophosphamide) (23) or TNF-α inhibitors may be used (level of evidence 4, strength of recommendation C). There is insufficient data to compare the respective efficacy of the various TNF-α inhibitors or of TNF-α inhibitors versus traditional immunosuppressive agents and IFN-α for the management of neurological ABD. However, it should be noted that so far infliximab has most frequently been used to treat ABD with parenchymal central nervous system involvement, with a favourable outcome in the majority of cases. TNF-α inhibitors that do not cross the brain-blood barrier such as pegylated certolizumab should be avoided.
- In patients with ABD-associated posterior uveitis and/or retinal vasculitis who do not respond or are intolerant to treatment with glucocorticoids (60 mg prednisone-equivalentand tapering), azathioprine (given at 2.5 mg/kg/day) and/or another immunosuppressive agent (usually cyclosporine given at 2-5 mg/kg/day) (23), biological agents may be used. Biological agents may also be used in patients on the above regimen who suffer repeated (≥2) flares or relapses upon tapering the glucocorticoid dose below 7.5 mg/day of prednisone-equivalent. Both TNF-α inhibitors (level of evidence 4, strength of recommendation C) and INF-α (level of evidence 1b, strength of recommendation A) may be used. TNF-α inhibitors may be used in combination with immunosuppressive agents, while IFN-α should be used on its own or in association with (usually low-dose) glucocorticoids. In cases of very severe, sight-threatening ocular inflammation (unilateral involvement with visual acuity <0.2 or bilateral involvement) a single infusion of infliximab may be given as first-line treatment.
- In patients with ABD-associated to intestinal inflammation who do not respond or are intolerant to treatment with glucocorticoids (60 mg prednisone-equivalent tapering) and azathioprine (2–2.5 mg/kg/day) (23), biological agents may be used. Biological agents may also be used in patients on the above regimen who suffer repeated (≥2) flares or relapses upon tapering the glucocorticoid dose below 7.5 mg/day of prednisone-equivalent (level of evidence 4, strength of recommendation C). It should be noted that among the biological agents, infliximab has most frequently been used, with a favourable outcome in the majority of cases.
- In patients with ABD-associated arthritis resistant to treatment with glucocorticoids at a dosage >5 mg/day of prednisone-equivalent and resistant or intolerant to at least two conventional agents such as colchicine, methotrexate or azathioprine (23;24), biological agents (TNF-α inhibitors [level of evidence 4, strength of recommendation C) or INF-α [level of evidence 1b, strength of recommendation A]) may be used.
- In patients with ABD-associated severe mucocutaneous manifestations despite treatment with glucocorticoids at a dosage >5 mg/day of prednisone-equivalent and at least two conventional agents such as colchicine, dapsone and azathioprine (25), biological agents (TNF-α inhibitors [level of evidence 4, strength of recommendation C; for oral ulcers and nodular lesions ETA level of evidence 1b, strength of recommendation A) or INF-α [level of evidence 1b, strength of recommendation A]) may be used.
- There is no reliable data on the efficacy of biological agents in ABD char-

acterised by vascular involvement. Treatment with biological agents can not be recommended in this patients' population.
- Whatever the indication, the effectiveness of biological therapy in ABD should be assessed within 4 months after treatment onset, and if no improvement has occurred, it should be discontinued.
- Patients with ABD who show lack or loss of efficacy or develop drug-specific reactions to a particular TNF-α inhibitor may be switched to another TNF-α inhibitor (level of evidence 4, strength of recommendation C)
- Patients with ABD refractory to glucocorticoids, synthetic disease-modifying anti-rheumatic drugs and at least one TNF-α inhibitor might be treated with tocilizumab (level of evidence 5, strength of recommendation D).

Giant cell arteritis

Giant cell arteritis (GCA), also known as temporal arteritis or Horton arteritis, is a vasculitis involving large- and medium-sized vessels with a predilection for the cranial arteries which predominantly affects patients aged fifty years or older (26). GCA therapy is largely based on GC, but there is some evidence suggesting that MTX (27) and AZA (28) may be used as steroid-sparing agents. In particular, in patients with longstanding GCA, MTX at a mean dose of 11 mg/week as add-on therapy to GC has been shown to reduce the risk of a first relapse by 35% and of a second relapse by 51%. In addition, adjunctive treatment with MTX reduced the cumulative exposure to GC. However, the superiority of the treatment effect of MTX over placebo became manifest only after a period of approximately 24 weeks, and there was no between-group difference in the occurrence of adverse events. The benefit conferred by AZA was even more modest (a slightly lower cumulative GC dose in the AZA compared to the placebo-treated arm) and of late onset.
Given the high rate of adverse events associated with GC therapy (29) and the limited efficacy of MTX and AZA as steroid-sparing agents, attempts have been made to explore new therapeutic avenues in GCA. Biological agents are the natural candidates for new therapies by virtue of their powerful anti-inflammatory and immunosuppressive properties and of their remarkable effectiveness in chronic inflammatory disorders such as rheumatoid arthritis. Among the various biological agents, TNF-α inhibitors are those most extensively studied. The rationale for TNF-α blockade in GCA is based on the observation of TNF-α expression in inflamed temporal arteries (30), which appears to correlate both with a strong systemic inflammatory response and with longer GC requirement (31). In addition, since B cells have been demonstrated in temporal artery samples from GCA patients (32), there have also been a few attempts to treat GCA by B-cell depletion. Herein, we have reviewed the published literature on biological therapy in GCA, and formulated recommendations for their use on the basis of the existing evidence.

Monotherapy with TNF-α inhibitors in giant cell arteritis

There are two published studies on the use of TNF-α inhibitors as monotherapy in three patients with GCA. One patient had previously been treated with GC, but had relapsed upon discontinuation of GC therapy due to adverse events. IFX given intravenously at a dose of 5 mg/kg at month 0, 1, 4 and 7 led to clinical remission and normalisation of inflammatory markers (33). Two other patients with newly diagnosed GCA without previous exposure to GC were treated with intravenous IFX 3 mg/kg at week 0, 2, and 6. Both patients attained a full clinical and laboratory remission, but both relapsed six weeks and three months after the last IFX infusion, respectively (34). One patient received an additional infusion of IFX with no improvement, whereas he subsequently responded to GC, while the other patient was commenced straightaway on GC with a favourable response.
These data may suggest a role for anti-TNF-α monotherapy in the early phase of the disease. On the other hand, the limited number of cases reported as well as the loss of efficacy in one patient upon retreatment with a TNF-α inhibitor invite to caution. It is also unclear whether anti-TNF-α monotherapy is able to prevent ischaemic complications. Finally, it is worth noting that anecdotal cases of patients developing GCA while receiving anti-TNF-α therapy have been reported (35, 36). For these reasons, we do not endorse the use of anti-TNF-α monotherapy in GCA.

TNF-α inhibitors as adjunctive therapy to glucocorticoids in recent-onset giant cell arteritis

The efficacy of TNF-α inhibitors in recent-onset GCA has been investigated in a RCT carried out in 44 patients with GCA of less than four weeks' duration in GC-induced remission (37). Sixteen patients were assigned to GC and placebo, and twenty-eight patients to GC and intravenous IFX 5 mg/kg at 0, 2, 6 weeks and subsequently 8-weekly. Prednisone was tapered according to a predefined schedule. Primary end-points were the number of relapse-free patients through week 22 and the incidence of adverse events. Secondary end-points included time to first relapse, cumulative GC dose, and the number of patients that remained relapse-free while the GC dosage was tapered to 10 mg/day. Relapses were defined as an increase in ESR plus at least one symptom or sign of GCA. In this trial, IFX therapy did not prove better than placebo for any outcome considered, leading to an early termination of the study at week 22. These results thus strongly suggest that anti-TNF-α therapy as add-on to GC is not more effective than placebo in recent-onset GCA.

TNF-α inhibitors in longstanding glucocorticoid-refractory giant cell arteritis

There is a RCT and a few reported cases on TNF-α blockade in patients with longstanding GC-refractory GCA.

– Randomised controlled trial of etanercept in giant cell arteritis

A RCT addressed the question of whether TNF-α inhibition by ETA might reduce GC exposure in GCA (38). Seventeen patients with refrac-

tory GCA requiring a prednisone dose greater than 10 mg/day for maintaining clinical remission and with at least one GC-related adverse event were randomised to ETA 25 mg twice weekly or placebo. The primary outcome measure was the proportion of patients no longer taking prednisone at 12 months. Secondary outcomes were the cumulative prednisone dose, the number of disease flares, the number of GC-related side effects or worsening of the previous side-effects. Patients in the ETA group were more successful in discontinuing prednisone therapy (although the difference did not reach significance) and required a significantly lower cumulative prednisone dose after 12 months of treatment. In addition, only one patient treated with ETA discontinued the study due to lack of efficacy compared to six patients in the placebo group. In contrast, there were no differences in the number and type of adverse events. Although the primary end point of the study was not met, possibly due to the small population of patients enrolled, overall the findings of this trial suggest some efficacy for TNF-α blockade by ETA in suppressing disease activity in refractory GCA. Thus, ETA may be tried in patients with GCA resistant to conventional treatment or with a chronic-relapsing course and significant GC requirement (≥7.5 mg of prednisone or its equivalent per day).

– Uncontrolled studies of TNF-α inhibitors in giant cell arteritis

We were able to identify five additional papers describing treatment of long-standing GCA with anti-TNF-α therapy (39-43). One paper described a patient in whom the diagnosis of GCA was not firmly established and was thus excluded from the analysis (43). Another paper reported a patient who suffered a relapse of GCA nearly two years after GC withdrawal and was successfully treated with high-dose prednisone and shortly thereafter with IFX 3 mg/kg replaced for maintenance by ETA 25 mg twice weekly (40). One patient with relapsing GCA of six months' duration despite treatment with prednisone 40 mg daily and MTX 7.5-15 mg weekly responded favourably to methylprednisolone pulse therapy and an increase in the prednisone dose to 60 mg/day. The patient was subsequently started on ADA (regimen not stated) with attainment of remission, while the prednisone dose could be tapered to 12.5 mg/day over 6 months (41). Another patient who had had GCA for over four years and had never been able to decrease the prednisone dose below 20 mg/day entered clinical and laboratory remission within 2-6 weeks of receiving IFX 3 mg/kg (given at week 0 and then at week 2, 6, 14, and 22), and was able to taper the prednisone dose to 10 mg/day by week 22 (39). Finally, there is a report of a series of four patients with GCA lasting 42 to 54 months who were unable to reduce their prednisone dose below 7.5-12.5 mg/day. After receiving IFX 3 mg/kg at week 0, 2, and 6, three of four patients entered prolonged remission, while GC therapy could be withdrawn (42).

Taken together, the results of these studies suggest that TNF-α blockade could be effective in at least part of the patients with GC-resistant GCA.

– Treatment of giant cell arteritis with the B-cell depleting monoclonal antibody rituximab

There are just two case reports on the use of rituximab in GCA. One patient had atypical clinical features and the diagnosis was not secured by a temporal artery biopsy, therefore this case report has not been considered for analysis (44). The other reported patient had active GCA with large-vessel involvement of several months' duration despite treatment with prednisone 15 mg/day (45). Treatment with RTX 1 g associated with cyclophosphamide 500 mg and methylprednisolone 100 mg intravenously led to successful B-cell depletion. After achieving B-cell depletion, the patient entered clinical remission sustained at 6-month follow-up, while inflammatory indices returned to normal, and large-vessel vasculitis as assessed by ^{18}Fluorodeoxyglucose positron emission tomography improved markedly.

As no other data is available on RTX in GCA, we feel that no recommendations can be made.

– Treatment of giant cell arteritis with the interleukin-6 receptor antagonist tocilizumab

The proinflammatory cytokine interleukin-6 (IL-6) is increasingly being recognised as a key molecule in the pathogenesis of large-vessel vasculitis including GCA. IL-6 is able to induce the production of acute-phase reactants and to cause constitutional manifestations, which are typical features of GCA (46). In addition, raised serum IL-6 levels have been shown to correlate with disease activity in GCA (47). Tocilizumab at a dose of 8 mg/kg/month proved able in a study to induce a rapid clinical and laboratory response including tapering of glucocorticoids in 5 patients with GCA (48). Similar efficacy has subsequently been reported in further 2 patients with GCA (49). However, it remains to be established whether tocilizumab is able to prevent ischaemic manifestations of GCA including visual loss.

Published guidance on the use of biological agents in giant cell arteritis

Recommendations on how to treat large-vessel vasculitis including giant cell arteritis have been published by the EULAR in 2008 (50). However, biological agents were not included in those recommendations.

On the basis of the literature available, we formulate the following recommendations:

- Biological (TNF-α inhibiting) agents can not be recommended as monotherapy (*i.e.* without glucocorticoids) for giant cell arteritis (GCA) because of insufficient evidence of efficacy. There is insufficient evidence to recommended the use of tocilizumab as monotherapy for GCA.
- Biological (TNF-α inhibiting) agents can not be recommended as first-line, add-on therapy to glucocorticoids in newly diagnosed GCA because of evidence of no to poor efficacy (level of evidence 1b, strength of recommendation A). There is insufficient evidence to recommend the use of tocilizumab as first-line, add-on therapy for GCA.
- Biological (TNF-α inhibiting) agents may be used in patients with GCA

with ≥2 flares or relapses despite adequate treatment with glucocorticoids and with ≥1 immunosuppressive agent unless contraindicated or not tolerated (level of evidence 4, strength of recommendation C). A flare is defined as the recurrence of ≥1 clinical manifestation in association with a raised erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], or both in patients taking >5 mg/day of prednisone-equivalent. A relapse is defined as the recurrence of ≥1 clinical manifestation in association with a raised ESR, CRP, or both in patients not taking glucocorticoids.

- Tocilizumab may be used in patients with GCA characterised by large-vessel involvement who incur ≥2 flares or relapses despite adequate treatment with glucocorticoids and with ≥1 immunosuppressive agent unless contraindicated or not tolerated (level of evidence 4, strength of recommendation C). A flare is defined as the recurrence of ≥1 clinical manifestation in association with a raised erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], or both in patients taking >5 mg/day of prednisone-equivalent. A relapse is defined as the recurrence of ≥1 clinical manifestation in association with a raised ESR, CRP, or both in patients not taking glucocorticoids.
  - There is no universally accepted "adequate glucocorticoid regimen" in GCA, but an example of an adequate regimen is treatment with initial doses of 40-60 mg (1 mg/kg in patients with ischaemic manifestations) prednisone-equivalent per day tapering by 5 mg every 1-2 weeks until a dose of 10 mg/day is reached, and subsequently by smaller decrements of 1 mg every 2-6 weeks under monitoring of clinical manifestations and of inflammatory markers.
  - Immunosuppressive agents that may be used in GCA include methotrexate (MTX) and azathioprine (AZA) (50). Although there is insufficient data to dictate the optimal dose and length of treatment, we recommend that MTX be used at a dosage of 15–20 mg/week and AZA be used at a dosage of 2–2.5 mg/kg/day for 4–6 months.
  - The effectiveness of biological therapy should be assessed within 4 months after treatment onset, and if no improvement has occurred, it should be discontinued.

Takayasu arteritis

Takayasu arteritis (TA) is a rare vasculitis which mainly involves the aorta and its major branches, causing stenoses, occlusions, and less frequently dilation and aneurysms of the affected vessels (51). GC are the mainstay of treatment, but cytotoxic agents are often required to control the inflammatory process. In patients refractory to combined GC and immunosuppressive therapy, biological agents have been used with variable success. Cyclophosphamide has also proved effective in a small sample of patients with resistant TA (52). However, in the light of the young age of many patients with TA and of the known toxicity of cyclophosphamide especially on gonadal function (53, 54), cyclophosphamide is very seldom used in TA (55).

– Treatment of Takayasu arteritis with TNF-α inhibitors

We identified two large case series, including a prospective open-label trial (56) and a retrospective review (57), plus a number of case reports or small series (58-62) describing patients mostly with refractory TA treated with TNF-α inhibitors. The main results of these papers are summarised in Table II. A total of 49 patients were reported, all of whom but one had refractory TA. Of these 49 patients, only 6 failed to adequately respond to anti-TNF-α therapy, i.e. did not achieve complete or partial remission. However, in a sizeable proportion of cases dose escalation was required to maintain clinical efficacy.

– Treatment of Takayasu arteritis with the B-cell depleting monoclonal antibody rituximab

A recent study described 3 patients with refractory TA successfully treated with RTX (63). Treatment with RTX resulted in clinical and laboratory remission in all patients.

As no other data is available to reliably document the efficacy of RTX in TA, we feel that no recommendations can be made on the use of RTX to treat refractory TA.

– Treatment of Takayasu arteritis with the interleukin-6 receptor antagonist tocilizumab

There is a case report of a patient with refractory TA successfully treated with the anti-IL-6 monoclonal antibody tocilizumab (64). Tocilizumab proved also effective in four further patients with TA reported by two independent study groups (48, 49). Altogether, one of the patients treated with tocilizumab was treatment-naïve and four had refractory TA. Finally, a response to TCZ has been described in a patient with TA refractory to TNF-α blockade (65).

On the basis of the literature results, we feel that biological (TNF-α inhibiting) agents may be tried in patients with TA resistant to GC and immunosuppressive therapy. Tocilizumab may also be used to treat resistant TA.

Published guidance on the use of biological agents in Takayasu arteritis

Recommendations on how to treat large-vessel vasculitis including Takayasu arteritis have been published by the EULAR in 2008 (50). However, biological agents were not included in those recommendations.

On the basis of the literature available, we formulate the following recommendations:

- Biological (TNF-α inhibiting) agents can not be recommended as monotherapy (*i.e.* without glucocorticoids) for Takayasu arteritis (TA) because of lack of evidence. There is yet insufficient evidence to recommended the use of tocilizumab as monotherapy for TA.
- Biological (TNF-α inhibiting) agents can not be recommended as first-line, add-on therapy to glucocorticoids in newly diagnosed TA because of lack of evidence. There is yet insufficient evidence to recommended the use of tocilizumab as first-line, add-on therapy for TA.

Table II. Case reports and case series on the use of biological (TNF-α blocking) agents in Takayasu arteritis.

Ref.	Pts	N/R	Study Drug (other drugs)	F'up	Outcome
(56)	15	R	7 patients ETA 25 mg twice weekly, 3 of whom switched later to IFX 8 patients IFX 3-5 mg/kg at week 0, 2, 6, and 4-8 weekly thereafter (14 patients on glucocorticoids, 11 patients on immunosuppressants)	3-51 months	10/15 complete remission sustained for 1-3.3 years without glucocorticoids 4/15 partial remission with a least 50% reduction in the prednisone dose 1/15 treatment failure 9/14 responders required an increase in anti-TNF-α dose
(57)	25	R	9 patients ETA 21 patients IFX at a mean dose 5 mg/kg every 6 weeks (all patients were treated with glucocorticoids and a mean of two immunosuppressants)	median 28 months	Of the 9 ETA treated patients, 4 had complete and 2 partial remission, while 3 failed to respond and were switched to IFX. Of the 4 patients who had a complete remission, one subsequently relapsed and was switched to IFX Of the 21 IFX treated patients, 12 had complete and 6 partial remission. 1 patient failed to respond, while IFX was withdrawn in 1 patient for adverse events and in 1 patient for other reasons
(62)	1	R	IFX 3 mg/kg (regimen not stated) (GC and MTX)	7 months	Prednisone dose could be decreased from 15 to 10 mg/day, while C-reactive protein decreased from 3 to 0.5 mg/ml
(61)	4	R3, N1	IFX 3 mg/kg at week 0, 2, 4, then 8-weekly (3 refractory patients GC + AZA or MTX, 1 newly diagnosed patient MTX)	24 months	3 out of 4 patients (including the newly diagnosed one) responded, but 2/3 responders required dose escalation
(58)	2	R	IFX 3 mg/kg at week 0, 2, 6, then 8-weekly (both patients GC and MTX)	1 8/12 1 14/12	Remission, prednisone discontinued in 1 patient
(59)	1	R	IFX 5 mg/kg at week 0, 2, 6, then 4-8 weekly (PDN 1 mg/kg/day tapering, MTX 15 mg/week)	2 years	Remission, PDN and MTX dose decreased
(60)	1	R	IFX 3 mg/kg at week 0, 2, 4 and 8, subsequently switched to ADA 40 mg eow (PDN 25 mg/day)	10 months	Clinical remission, normalisation of ESR, PDN tapered to 7 mg/day

N/R (New/refractory): "refractory" means patients with insufficient or no response to treatment with glucocorticoids and/or at least 1 immunosuppressant, "new (treatment)" means patients who have not previously been treated or who have previously been successfully treated, but in whom treatment was withdrawn for reasons other than lack of efficacy prior to receiving biological agents. For a full list of the abbreviations used in this Table, please refer to "List of abbreviations used in this paper and in the Tables (in alphabetical order)" in the main text.

- Biological (TNF-α inhibiting) agents may be used in patients with TA with persistently active disease for ≥6 months or with ≥2 flares or relapses despite adequate treatment with glucocorticoids and with ≥1 immunosuppressive agent unless contraindicated or not tolerated (level of evidence 4, strength of recommendation C). A flare is defined as the fulfillment of the Kerr criteria after attaining remission and/or as the appearance of a new vascular lesion (stenosis, obstruction or aneurysm) and/or the worsening of a previously documented vascular lesion (stenosis or aneurysm) due to active disease on computerised tomography angiography, magnetic resonance angiography, or conventional angiography, in patients taking >5 mg/day of prednisone-equivalent. A relapse is defined as the fulfillment of the Kerr criteria after attaining remission and/or as the appearance of a new vascular lesion (stenosis, obstruction or aneurysm) and/or the worsening of a previously documented vascular lesion (stenosis or aneurysm) on computerised tomography angiography, magnetic resonance angiography, or conventional angiography, in patients not taking glucocorticoids.
- Tocilizumab may be used in patients with TA with persistently active disease for ≥6 months or with ≥2 flares or relapses despite adequate treatment with glucocorticoids and with ≥1 immunosuppressive agent unless contraindicated or not tolerated (level of evidence 4, strength of recommendation C).
  - There is no universally accepted "adequate glucocorticoid regimen" in TA, but an example of an adequate regimen is treatment with initial doses of 60 mg or ≥1 mg/kg prednisone-equivalent per day with gradual tapering by 5 mg every 1–2 weeks until a dose of 10 mg/day is reached, and subsequently by smaller decrements of 1 mg every 2–6 weeks under monitoring of clinical manifestations and of inflammatory markers (66).
  - Immunosuppressive agents that may be used in TA include methotrexate (MTX) (67), azathioprine (AZA) (68) and mofetil mycophenolate (MMF) (69). Although there is insufficient data to dictate the optimal dose and length of treatment, we recommend that MTX be used at a dosage of 20 mg/week, AZA be used at a dosage of 2–2.5 mg/kg/day, and MMF be used at a dosage of 2 g/day for 4–6 months.
  - The effectiveness of biological therapy should be assessed within 4 months after treatment onset, and if no improvement has occurred, it should be discontinued.

Cogan's syndrome

Cogan's syndrome is a rare vasculitis whose hallmark features are interstitial keratitis and audiovestibular manifestations resembling Meniere disease. GC and various immunosuppressive drugs are empirically used, but response to treatment is variable (70).

There is no controlled data on the use of biological agents in Cogan's syndrome. We identified five papers describing nine patients with Cogan's syndrome treated with TNF-α inhibitors (71-75). All patients had been treated with GC and some had also received cyclophosphamide with or without other immunosuppressive agents with partial or no response. IFX was used in six patients mostly at 3 mg/kg with variable intravenous administration schemes, while ETA was used in three patients at 25 mg subcutaneously twice weekly. Of the six patients treated with IFX, one attained full remission (71), four improved significantly, and only one (72) failed to respond. Of the three patients who received ETA, word recognition scores (a parameter of hearing function) improved in two patients. GC dose could be tapered (71, 75), or GC discontinued (73) in all reported cases.

This limited evidence suggests that TNF-α blockade may be beneficial in patients with refractory Cogan's syndrome.

On the basis of the literature available, we formulate the following recommendations:

- Biological (TNF-α inhibiting) agents can not be recommended as monotherapy (*i.e.* without glucocorticoids) for Cogan's syndrome because of lack of evidence.
- Biological (TNF-α inhibiting) agents can not be recommended as first-line, add-on therapy to glucocorticoids in newly diagnosed Cogan's syndrome because of lack of evidence.
- Biological (TNF-α inhibiting) agents may be used in patients with Cogan's syndrome with unremitting or progressive audiovestibular or ocular manifestations on two assessments at least 2 weeks apart or with ≥2 flares or relapses despite adequate treatment with glucocorticoids and with immunosuppressive therapy unless contraindicated or not tolerated (level of evidence 4, strength of recommendation D).
  - Active audiovestibular and ocular manifestations are defined as clinical symptoms confirmed by the appropriate investigations (audiogram for audiovestibular manifestations and ophtalmologist assessment for ocular manifestations).
  - There is no universally accepted "adequate glucocorticoid regimen" in Cogan's syndrome, but an example of an adequate regimen is treatment with initial doses of 60 mg or ≥1 mg/kg prednisone-equivalent per day (with or without methylprednisolone pulses at treatment onset) with subsequent gradual tapering.
  - Immunosuppressive therapy of empirical efficacy may include cyclophosphamide and azathioprine (70).
  - The effectiveness of biological therapy should be assessed within 4 months after treatment onset, and if no improvement has occurred, it should be discontinued.
  - There is no comparative data on the efficacy of the different anti-TNF-α inhibitors for Cogan's syndrome, but infliximab has mostly been used to treat this condition.

Primary angiitis of the central nervous system

Primary angiitis of the central nervous system (PACNS) is a rare vasculitis which affects exclusively the central nervous system (76). GC are considered the mainstay of treatment for PACNS, but immunosuppressive agents are required in over half of cases, with cyclophosphamide being the drug most often used (76). However, despite aggressive treatment, approximately one-fifth of patients show no favourable clinical response (76).

There is a single report in the published literature on two patients with refractory PACNS who received anti-TNF-α therapy (77). Indication for anti-TNF-α therapy was progressive deterioration of neurological status in one case and relapsing disease in the other. One patient received IFX 5 mg/kg as single intravenous infusion and the other ETA 25 mg weekly for twenty months, subsequently switched to 25 mg/kg once weekly for eight months. Both patients also received GC, in one case associated with cyclophosphamide followed by azathioprine. Both patients responded clinically to anti-TNF-α therapy, while MRI showed no evidence of new lesions in one case and reduction in previous active lesions in the other. No relapses have occurred at follow-up of 34 and 60 months, respectively.

Although the evidence in favour of anti-TNF-α is only anecdotal, these two well-documented cases suggest that TNF-α inhibitors may be tried in patients with PACNS who fail to respond to GC and cyclophosphamide.

On the basis of the literature available, we formulate the following recommendations:

- Biological (TNF-α inhibiting) agents can not be recommended as monotherapy (*i.e.* without glucocorticoids) for primary angiitis of the central nervous system (PACNS) because of lack of evidence.
- Biological (TNF-α inhibiting) agents can not be recommended as first-line, add-on therapy to glucocorticoids in newly diagnosed PACNS because of lack of evidence.
- Biological (TNF-α inhibiting) agents may be used in patients with PACNS with persistently active disease (unremitting or progressive clinical neurological deterioration with evidence of active lesions on magnetic resonance imaging [MRI]) despite treatment with glucocorticoids at adequate doses and immunosuppressive therapy (76) unless contraindicated or not tolerated (level of evidence 4, strength of recommendation C). Biological agents may also be used in patients on the above regimen who suffer ≥2 flares or relapses upon tapering the glucocorticoid dose below 7.5 mg/day.
  - There is no universally accepted "adequate glucocorticoid regimen" in PACNS, but an example of an adequate regimen is treatment with initial doses of 60 mg or ≥1 mg/kg prednisone-equivalent per day (with or without methylprednisolone pulses at

treatment onset) with subsequent gradual tapering.
- Immunosuppressive therapy of empirical efficacy includes cyclophosphamide (2 mg/kg/day orally for up to 2 months or 1 g/m^2 monthly for up to 6 months) (76). For maintenance therapy, immunosuppressive agents such as AZA may be considered.
- The effectiveness of biological therapy should be assessed within 4 months after treatment onset, and if no improvement has occurred, it should be discontinued.

List of abbreviations used in this paper and in the Tables
(in alphabetical order)
ABD: Adamantiades-Behçet's disease
ADA: adalimumab
AZA: azathioprine
CME: cystoid macular oedema
CNS: central nervous system
CR: complete remission
CYC: cyclophosphamide
eow: every other week
ESR: erythrocyte sedimentation rate
ETA: etanercept
F'up: follow-up
GC: glucocorticoids
GCA: giant cell arteritis
IFX: infliximab
IFN: interferon
IL: interleukin
IS: immunosuppressants
IU: international units
MRI: magnetic resonance imaging
MTX: methotrexate
N: new [treatment]
PACNS: primary angiitis of the central nervous system
PDN: prednisone
PR: partial remission
PTS: patients
R: refractory
RCT: randomised controlled trial
Ref: reference
RTX: rituximab
SD: standard deviation
TA: Takayasu arteritis
TNF-α: tumour necrosis factor α
VA: visual acuity

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