
Recommendations for the use of biologic therapy from the Italian Society for Rheumatology: off-label use

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ABSTRACT

The advent of biological agents has provided further opportunities to treat resistant or relapsing rheumatic diseases, with robust data for rheumatoid arthritis and spondyloarthritis coming from randomised controlled trials. However there are data also on other rare inflammatory rheumatic diseases even if the evidence available may be heterogeneous and/or controversial. Another challenging scenario is represented by diseases that are not uncommon, but that may present with multiple manifestations and prove resistant to conventional therapies, thus requiring the use of biological agents.

To assist physicians in making correct therapeutic choices in such cases, the Italian Society for Rheumatology (SIR) has developed specific recommendations for the use of biological agents in rare disease or for the off-label use of such agents in refractory inflammatory disorders.

Introduction

To date, glucocorticoids (GC) and immunosuppressive agents represent the cornerstone of treatment of chronic inflammatory rheumatic disorders. However, some patients fail to adequately respond to standard treatment. The advent of biological agents has provided further opportunities to treat resistant or relapsing cases, but these drugs are expensive and not entirely free from adverse events. In addition, the efficacy of these agents may vary depending on the treated condition. Therefore, there is a widespread perception that their use should be based on sound clinical data, mostly derived from randomised controlled trials (RCT). Unfortunately, because some inflammatory rheumatic disorders are quite rare, properly designed RCTs on them may be lacking. In such cases, therapeutic decisions inevitably rely on personal experience, results from uncontrolled observations,

and expert opinion (1-3). At the same time, the evidence available may be heterogeneous, controversial, or simply too complex to sift through. Another challenging scenario is represented by diseases that are not uncommon, but that may present with multiple manifestations and prove resistant to conventional therapies, thus requiring the use of biological agents. In both cases, the treating physician may feel uneasy about making decisions in clinical practice.

To assist physicians in making correct therapeutic choices in such cases, the Italian Society for Rheumatology (SIR) has developed specific recommendations for the use of biological agents in rare disease or for the off-label use of such agents in refractory inflammatory disorders. These include small- and large-vessel vasculitides, systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), idiopathic inflammatory myopathies (IIM), polymyalgia rheumatica (PMR), systemic sclerosis (SSc), sarcoidosis, adult-onset Still's disease (AOSD), gout and pseudogout, and inflammatory eye diseases. Intra-articular administration of anti-TNF agents in arthritis is also dealt with in this chapter.

To obtain evidence on the use of biological agents in the above disorders, PubMed search of relevant papers (until November 2009) was conducted using the appropriate key words for each treatment agent and each disease, respectively. The retrieved papers were included in the analysis if they were pertinent to the disease and treatments considered, if they were in English, if the diagnosis was reliably established, if the cases reported were adult cases (>18 years old), and if sufficient information could be extracted with regard to treatment efficacy. Editorials, review articles, and author's replies have not been considered. Relevant data recently presented as abstracts and/or during

meeting sessions have also been taken in consideration. Information about the safety profile of biological agents is published in a separate chapter, but important emerging issues are also mentioned herein whenever appropriate.

Levels of evidence have been assigned to the papers retrieved, and the strength of the recommendations has been graded according to the levels of evidence (4). However, since the cost of new therapies must be rigorously examined in these financially challenging times, in the elaboration of recommendations we have also taken into account the perceived global cost/benefit ratio, in line with the recommendations and guidelines by other international Societies.

Systemic lupus erythematosus

a) *Off-label rituximab therapy*

There are two RCTs conducted in patients with refractory SLE, none of which has shown a clear benefit of rituximab (RTX) over and above that provided by standard therapy in renal and in extra-renal manifestations. The LUNAR (LUPus Nephritis Assessment with Rituximab) study compared the addition of RTX (1000 mg on days 1, 15, 168 and 182) or a matched placebo to GC and mycophenolate mofetil (MMF) given intravenously at target dose of 3 g/day in 144 patients with active proliferative lupus nephritis. There was no significant between-group difference in the primary end point of complete or partial renal response, but only 1 RTX compared to 8 placebo patients required a new immunosuppressive agent added by 52 weeks (5). The incidence of serious adverse events (SAE) was comparable in the two arms, although leukopenia (12.3% vs. 4.2%), neutropenia (5.5% vs. 1.4%) and hypotension (11% vs. 4.2%) were more frequent in the RTX compared to the placebo arm.

The EXPLORER (Study to Evaluate the Efficacy and Safety of Rituximab in Patients With Severe Systemic Lupus Erythematosus) study recruited 257 patients with moderate to severe non-renal SLE and compared RTX (1000 mg at days 1, 15, 168 and 182) with placebo (PBO). GC 0.5–1.0 mg/kg were tapered to 10 mg daily by week 10. There was

no difference between RTX and PBO in the achievement of primary major and partial clinical response (defined by the British Isles Assessment Group [BILAG] [6]) and secondary end-points at 52 weeks of follow-up, although RTX significantly improved anti-dsDNA and complement levels (7). The incidence of adverse events (AE) was balanced between groups, with severe infectious complications being more frequent in placebo than in RTX treated patients (17% vs. 9.5%, respectively) and neutropenia being more frequent in the RTX group (7.7% vs. 3.4%).

The remaining published data on RTX in SLE derives from uncontrolled observations, which mostly showed efficacy of RTX on systemic, renal, haematological, articular, muco-cutaneous, cardio-pulmonary, neuropsychiatric features, and GC requirements. A possible explanation for the discrepancy between the results of the two RCTs quoted above and those of the uncontrolled reports may reside in the considerable immunosuppression used in the RCT, which might have overridden RTX-related effects. Overall, the impression is that RTX could be useful in selected cases of refractory SLE patients, although long-term data is not yet available.

The most frequently used RTX regimen is that recommended for the treatment of low-grade non-Hodgkin's lymphoma (9) (375 mg/m², 4-weekly intravenous administrations) followed by the administration protocol used in rheumatoid arthritis (10) (1000 mg 2 weeks apart). In all cases RTX was administered together with oral or intravenous GC and in almost half of the cases concomitantly with intravenous cyclophosphamide (CYC) mostly at 500 or 750 mg/m². Although the addition of CYC to RTX makes it difficult to determine to what extent the clinical responses observed were actually due to RTX, this regimen appeared to provide clinical benefits.

Escalation studies have shown no clear association between different RTX therapeutic regimens and clinical efficacy, safety, and B cell depletion in SLE patients (11–17).

Globally, at least one third of patients experienced clinical relapses on aver-

age 12 months after the first RTX administration, especially within the first 6 months (18, 19). The high observed frequency of relapses might be due to selection of patients, who had refractory and often severe disease. Available data of re-treated patients showed a good clinical response in almost 80% of cases, very close to that observed for initial therapy, with a trend of more rapid and persistent clinical response, suggesting that re-treatment may provide additional benefit (19–21).

On the basis of the available data, we suggest the following recommendations:

- Rituximab is not recommended as first-line therapy in patients with SLE Disease Activity Index (SLEDAI) (level of evidence Ib, strength of recommendation A).
- In patients with active SLE (SLEDAI > 8 and/or one “A” or two “B” items on BILAG) whose disease has failed to respond to standard immunosuppressive therapies (GC plus one immunosuppressive agent), rituximab might be considered as adjunctive treatment (level of evidence IIa, strength of recommendation B).
- In the case of clinical relapse, rituximab re-treatment with the same initial therapeutic scheme appears to be efficacious and safe with a trend toward more rapid and persistent clinical benefit over time (level of evidence IIb, strength of recommendation B).

– *Specific SLE organ involvement:*

• *Lupus nephritis*

A RCT assessed the efficacy of combined RTX and CYC therapy *versus* RTX alone in patients with proliferative lupus nephritis. Nine patients received RTX alone (1000 mg 2 weeks apart), while 10 were treated with RTX and CYC (750 mg/m² on day 1 in association with RTX administration). All patients also received pulse GC followed by oral GC (22). Combined therapy did not prove superior to RTX monotherapy in terms of clinical, laboratory, and histological outcomes. These results suggest that RTX could be efficacious even without concomitant CYC administration in lupus nephritis.

In contrast with the results from the LUNAR RCT, in several open studies RTX induced a complete or partial therapeutic response of 91% in 191 reported patients with lupus nephritis (23-27). In particular, RTX therapy improved markers of renal involvement including serum creatinine, albumin levels, 24-hour urinary protein excretion, haematuria and, in the few cases where were available, histological findings (25, 27, 29).

The most common therapeutic regimen was the lymphoma RTX scheme in association with intravenous CYC and pulse GC followed by step-down oral administration (25, 27), although other RTX schemes have also been reported (23, 24, 28). Limited data suggest efficacy of RTX associated with immunosuppressants different from CYC, such as azathioprine (AZA) and MMF (11, 26). Maintenance therapy after RTX induction therapy mainly consisted of low-dose prednisone and oral immunosuppressive agents (mostly MMF and AZA) (26, 29).

RTX has also been used as monotherapy with background GC only. In a recent prospective trial 20 patients with refractory lupus nephritis despite GC treatment achieved clinical remission with RTX induction monotherapy (1000 mg at baseline and after two weeks) followed by MMF maintenance therapy. This regimen was well tolerated and allowed progressive tapering of the GC dose or even GC withdrawal (29).

RTX also appears to hold promise in patients with renal insufficiency due to severe lupus nephritis. In a recent retrospective analysis, RTX (375 mg/m² weekly for 4 weeks) was given as induction and maintenance therapy in association with immunosuppressive agents and oral GC to 20 patients with severe refractory lupus nephritis (histologic classes III, IV, V according to WHO classification) (30). After two years of follow-up, 60% patients achieved a partial or complete renal response with a concomitant significant decrease in oral GC intake. Five patients were treatment failures, 4 of whom underwent chronic haemodialysis. Ten patients received repeated RTX infusions as maintenance therapy with clinical benefit. In all nine

patients for whom repeated biopsies were available at the end of the follow up, a decrease in histologic activity was observed, even in non-responders. Lack of clinical renal remission was significantly associated with the absence of B cell depletion one month after RTX initiation. However, failure to respond to RTX despite achievement of B cell depletion has also been reported (31). Results from a case report suggest that RTX might be safely used in haemodialysis patients, in case of relapsing SLE flares not sufficiently controlled by standard treatment (32). RTX does not appear to be eliminated by haemodialysis.

On the basis of the available data, we formulated the following recommendations:

- Rituximab may be considered as induction therapy for patients with active lupus nephritis that have failed glucocorticoids and immunosuppressive agents including pulse cyclophosphamide (level of evidence IIa, strength of recommendation B).
- The addition of cyclophosphamide to rituximab is not recommended (level of evidence Ib, strength of recommendation A).
- Immunosuppressants, particularly mofetil mycophenolate and azathioprine, should be considered as maintenance therapy after RTX induction (level of evidence IIb, strength of recommendation B).
- Rituximab in association with glucocorticoids and/or immunosuppressive agents may be used as induction and maintenance therapy even in case of active lupus nephritis complicated by mild-to-severe renal insufficiency (level of evidence IIb, strength of recommendation B). No dose adjustment of RTX is required (level of evidence IV, strength of recommendation C)
- Rituximab is not recommended as adjunctive therapy in refractory rapidly progressive glomerulonephritis because of lack of evidence of efficacy (level of evidence IV, strength of recommendation C).

• Neuropsychiatric SLE

The largest case series of SLE patients with neuropsychiatric (NPS) involve-

ment treated with RTX contained 10 patients with refractory central nervous system (CNS) lesions. Clinical response to RTX was noted for a welter of manifestations including confusional state, seizures, psychosis, and cognitive dysfunction virtually in all cases over 6 months, while ongoing immunosuppressive agents could be tapered or withdrawn (33). Re-treatment was efficacious in 2 relapsing cases. Maintenance RTX therapy (three monthly RTX infusions at a dose of 375 mg/m²) was also efficacious in two cases (34). Rapid and satisfactory responses in terms of neuropsychiatric involvement have also been reported by two other open-label studies (15, 16) and case reports (Table I).

• Haematological features

An overall favourable clinical response was observed in about 94% of RTX-treated patients with haematologic alterations (in some cases refractory to standard therapy) attributable to SLE, including thrombocytopenia and haemolytic anaemia (14, 16, 18, 30, 35-37) (Table II). In most cases, RTX was given with conventional immunosuppressants and GC. Reduction or disappearance of pathogenic autoantibodies such as anti-platelet antibodies have occasionally been reported. On the other hand, in two patients with the antiphospholipid syndrome RTX treatment was linked to thrombotic AE possibly due to immune complexes of RTX and anti-RTX antibodies (38).

• Mucosal and skin features

In most studies, muco-cutaneous features were associated with other SLE manifestations, but were not the primary indication for RTX use. However, successful use of RTX for SLE skin manifestations including oral ulcers, cutaneous vasculitis, and alopecia has been described (Table III).

On the basis of the available data we formulated the following recommendations:

- In patients with severe neuropsychiatric SLE refractory to glucocorticoids and standard immunosuppressive agents add-on rituximab may be considered (level of evidence IV, strength of recommendation C).

- Rituximab maintenance therapy might be considered in refractory patients that have responded to rituximab induction therapy (level of evidence IV, strength of recommendation C) in patients with severe neuropsychiatric SLE refractory to immunosuppressants.
- Rituximab may be considered as adjunctive therapy to treat thrombocytopenia and autoimmune haemolytic anaemia (level of evidence IV, strength of recommendation C).
- In SLE patients with severe mucocutaneous involvement refractory to multiple immunosuppressive agents, rituximab may be considered as adjunctive therapy (level of evidence IV, strength of recommendation C).

b) Anti-TNF- α agents off-label therapy

There is limited experience with TNF- α inhibitors in SLE. Uncontrolled observations suggest some efficacy of infliximab in lupus nephritis (39–41). In a small pilot RCT including 27 patients (9 assigned to the treatment arm, 18 to the control group) with active and refractory SLE, a brief course of infliximab (5 doses of 3 mg/kg at 0, 2, 6 and then every 8 weeks) in association with ongoing immunosuppressive treatments resulted in several beneficial effects including consistent reduction of daily oral GC requirement and significant improvement in SLEDAI scores at 6 months of follow-up in comparison to control group. No greater improvement was demonstrated in laboratory or immunological parameters in the same period, including measures of renal function (24-hours urine protein and urine sediment) (42). In 5 patients continuing to receive infliximab positive effects were seen especially on mucocutaneous features, arthritis and serositis, but no conclusions could be drawn on specific organ involvement due to the limited number of subjects enrolled. On a note of caution, increased autoantibody production has been reported (43, 44). Regarding the use of etanercept in SLE, two cases reported efficacy in subcutaneous lupus (45, 46) and in a pregnant woman with severe lupus nephritis that experienced a complete remission with

Table I. SLE-related case reports and series on neuropsychiatric involvement.

Ref.	Pts	N/R	Features	Study-drug (DMARDs/GC)	Follow-up	Outcome
Saito (208)	1	R	CNS, K	RTX (+/+)	7 ms	CR
Tokunaga (209)	5	R	CNS, PNS	RTX (+/+)	7 ms	5/5 CR
Amstrong (210)	1	R	CNS	RTX (+/+)	45 ds	PR

Ref: bibliographic references; Pts: patients number; DMARDs: disease modifying anti-rheumatic drugs; GC: glucocorticoids; RTX: rituximab; N/R: new case/refractory; CR: complete remission; PR: partial remission; CNS: central nervous system; PNS: peripheral nervous system; K: kidney involvement; ms: months; ds: days.

Table II. SLE-related case reports and series on haematological involvement.

Ref.	Pts	N/R	Features	Study-drug (DMARDs/GC)	Follow-up	Outcome
Perrotta (211)	1	R	HA	RTX (+/+)	7 ms	CR
Kneitz (212)	2	R	IT	RTX (-/+)	4 ms	1 CR; 1 F
Limal (213)	1	R	TTP anti ADAMTS13+	RTX (+/+); + PE	11 ms	CR
Kamiya (214)	1	R	HPS, then refractory TTP antiADAMTS13-	RTX (+/+); + PE	100 ds	CR for TTP (HPS relapse)
Lehembre (215)	1	R	IT, multisystemic TB	RTX (+/-)	29 ms	CR
Fukushima (216)	1	R	AT	RTX (+/+)	11 ms	CR
Kittaka (217)	1	R	Evans syndrome	RTX (+/+)	1 ms	CR
Kothani (218)	1	R	CAD	RTX (+/+)	8 ms	CR
Ahn (219)	1	R	Severe APS	RTX + PE	15 ms	CR

HA: haemolytic anaemia; IT: immune thrombocytopenia; TTP: thrombotic thrombocytopenic purpura; PE: plasma-exchange; HPS: haemophagocytic syndrome; TB: tuberculosis; AT: amegakaryocytic thrombocytopenia; CAD: cold agglutinin disease; APS: anti-phospholipid syndrome; CR: complete remission; F: failure; R: refractory case.

Table III. SLE-related case reports and series on cutaneous involvement.

Ref.	Pts	N/R	Features	Study-drug (DMARDs/GC)	Follow-up	Outcome
Kieu (220)	1	R	SCLE	RTX (+/+)	2 ys	CR
Uthman (221)	1	R	SCLE	RTX (+/+)	6 ms	CR
Risselada (222)	2	R	SLE	RTX (+/+)	4 ms	2/2 CR
McArdle (223)	1	R	LEP	RTX (+/+)	2 ms	CR

SCLE: subacute cutaneous lupus erythematosus; LEP: lupus erythematosus profundus; CR: complete remission; R: refractory case; ms: months.

etanercept, plasma exchange (PE) and high-dose intravenous immunoglobulins (47).

On the basis of these data, we formulated the following recommendations:

- TNF- α inhibitors are not recommended to treat manifestations of systemic lupus erythematosus because of limited evidence of efficacy (level of evidence IV, strength of evidence C).

c) Anakinra off-label therapy

There is a case series reporting treatment efficacy of subcutaneous (sc) 100 mg Anakinra daily in 4 SLE patients with active non-erosive polyarthritis refractory to previous treatment with GC (<15mg/die) and several disease-modifying anti-rheumatic drugs (DMARDs) (48). Temporary subjective and objective benefits were seen in all patients treated. However, after 12 weeks clini-

cal activity tended to increase again and two patients required switching to a different treatment because of loss of efficacy.

On the basis of the available data, we formulated the following recommendations:

- Treatment with anakinra for active systemic lupus erythematosus-related non-erosive polyarthritis cannot be recommended due to insufficient evidence of clinical efficacy (level of evidence IV, strength of recommendation D).

ANCA associated vasculitides

a) Rituximab off-label therapy

The current standard treatment in ANCA-associated vasculitides (AAV) is an aggressive GC regimen combined with CYC. Unfortunately, the clinical outcome of such therapy shows that 10% patients do not experience clinical remission and about 50% patients relapse (49). In addition, conventional therapy has some serious AE which limit its long-term use.

Encouraging results come from the study “Rituximab for the treatment of Wegener’s Granulomatosis and Microscopic Polyangiitis (RAVE)” (50). The study was conducted as a non-inferiority randomised, double-blind, placebo-controlled trial comparing RTX (375 mg/m² intravenous weekly for 4 weeks) with daily oral CYC (2 mg/kg/day) for remission-induction in 197 ANCA-positive patients with severe, active (Birmighan Vasculitis Activity Score validated for WG, BVAS/WG [51] score >3) Wegener Granulomatosis or Microscopic Polyangiitis (3:1 randomisation ratio). Almost half patients in each arm had new-onset disease, while the others had a chronic relapsing course with disease flares severe enough to require CYC. Once remission was achieved, CYC was replaced with AZA, while the same GC regimen was used in both treatment arms, consisting of 1–3 g intravenous methylprednisolone followed by oral prednisolone 1 mg/kg/day, reduced to 40 mg/day by 1 month, and then tapered and withdrawn by month 6. The primary end point of complete disease remission, defined as a BVAS/

Table IV. Other SLE-related case reports and series on further organ involvement.

Ref.	Pts	N/R	Features	Study-drug (DMARDs/GC)	Follow-up	Outcome
Reynolds (36)	3	R	L	RTX (+/+)	6 ms	1CR,2 PR
Lim (224)	1	R	L	RTX (+/+)	5 ms	CR
Nellessen (225)	1	R	DAH	RTX (+/+); + PE	3 ys	CR
Pinto (226)	1	R	PH, K	RTX (+/+)	n.s.	CR
Torrente-Segarra (227)	1	R	AD	RTX (+/+)	2 ms	CR
Simon (228)	1	N	DLBCL	R-CHOP	1 ys	CR
Henningan (229)	1	R	PAH	RTX (-/+)	2 ys	PR
Waite (230)	1	R	GIV	RTX (+/+)	2 ys	CR
Hickman (231)	1	R	RV	RTX (+/+)	1 ys	PR
Ideguchi (232)	1	R	HLH	Infliximab (+/+)	15 ds	CR
Hayat (233)	1	R	Sy	Infliximab (+/+)	1 ys	CR
Hayat (40)	1	R	K	Infliximab (+/+)	6 ms	CR
Naretto (234)	1	R	Skin	Infliximab (+/+)	6 ms	CR

L: lung involvement; DAH: diffuse alveolar haemorrhage; PH: pulmonary haemorrhage; AD: articular disease; DLBCL: diffuse large B cell non-Hodgkin lymphoma; PAH: pulmonary arterial hypertension; GIV: gastrointestinal vasculitis; RV: retinal vasculitis; HLH: haemophagocytic lymphohistiocytosis; Sy: systemic involvement; K: kidney; n.s. (abs): not specified because only abstract available; N: new case; R: refractory case; CR: complete response; PR: partial response; PE: plasma exchange; R-CHOP: RTX + cyclophosphamide, doxorubicin, vincristine, prednisone.

WG equal to 0 in the absence of prednisolone, was achieved by 64% of patients in the RTX arm compared with 53% in the CYC group at month 6, the between-group differences being not significant. In addition, in a subgroup analysis, among patients with relapsing disease at baseline, RTX was more efficacious than CYC: 67% patients in RTX group reached the primary end point as compared with only 42% in the control arm. Rates of disease flare and AE were similar in the two groups. A limitation of this study is the exclusion of patients with severe alveolar haemorrhage requiring ventilatory support and of those with advanced renal dysfunction (serum creatinine >4.0 mg/dl). These data suggest that RTX is not inferior to conventional therapy in inducing disease remission by 6 months of follow-up and thus it could serve as an alternative strategy in this setting. In the RITUXVAS study (randomised trial of RTX *versus* CYC for ANCA-associated vasculitis) 44 patients with newly diagnosed AAV and renal involvement were randomly assigned, in a 3:1 ratio, to either the RTX or to the control group. Both groups received intravenous methylprednisolone (at a dose of 1 g) and the same oral GC regimen (1 mg per kilogram per day initially, with a reduction to 5 mg per

day at the end of 6 months). Patients in the RTX group received RTX at a dose of 375 mg/m² per week, for 4 consecutive weeks, and intravenous CYC at a dose of 15 mg per kilogram with the first and third RTX infusions; these patients did not receive AZA to maintain remission. For patients in the RTX group who had progressive disease within the first 6 months, a third dose of intravenous CYC (at a dose of 15 mg per kilogram) was permitted. Patients in the control group received a validated regimen of intravenous CYC for 3 to 6 months, followed by AZA. Further treatment with RTX or CYC was permitted in cases of relapse. Relapses occurring before a minimum of 6 months of sustained remission were considered failures with respect to the primary efficacy end point. The study’s primary end point, sustained remission (BVAS of 0 for 6 months) at 12 months was achieved by 76% of patients treated with RTX, and by 82% of patients treated with CYC (difference non-significant). Deaths were 18% in both arms. AE were also similar in both arms (52). Like the RAVE, this study included only ANCA-positive patients. Therefore, the results of this study may not be generalised to ANCA-negative patients. Unlike the RAVE, in this study patients randomised to rituximab

also received at least two doses of intravenous cyclophosphamide, whereas in the RAVE trial patients randomly assigned to rituximab did not receive cyclophosphamide. Despite these differences in study protocols, the RAVE and the RITUXVAS both showed equipotency of RTX compared to CYC.

In addition to these RCTs, the use of RTX in AAV patients, with refractory disease and/or SAE related to standard immunosuppressive treatments, is globally reported by 6 retrospective analyses (53-58), 4 prospective trials (19, 59-61), and several case series and reports (Table V). Data are available mostly for patients with Wegener's granulomatosis (n=142), but fewer cases of microscopic polyangiitis (25 patients) and Churg-Strauss syndrome (11 patients) have also been reported (19, 53, 55, 58, 60). Most patients had severe (BVAS-WG>3 or more, BVAS>8 for AAV other than WG) and refractory disease despite treatment with the highest tolerated dose of CYC given in combination with prednisolone therapy for at least 6 months or having contraindications for its use. In the majority of cases, a significant clinical improvement or even clinical remission following RTX therapy was achieved according to the BVAS index (64). Induction of remission was often rapid and persistent. RTX was usually given with the lymphoma scheme, but no RTX regimen proved clearly superior. In all cases GC (from 0.5 to 2 mg/kg/day) were co-administered, mostly in association with other DMARDs.

Regarding the efficacy of RTX in the patients' subset characterised by predominantly granulomatous manifestations the evidence is partially conflicting. Omdal *et al.* and Aries *et al.* suggested poorer responsiveness to RTX of patients with predominantly granulomatous manifestations, particularly orbital pseudotumour (54, 59). On the contrary, Seo *et al.* found RTX equally effective in inducing and sustaining clinical remission in patients with generalised vasculitis as in those with granulomatous disease manifestations, like chronic sinusitis, pulmonary nodules, orbital pseudotumour, and subglottic stenosis (65).

Table V. AAV-related case reports and series with off-label RTX.

Ref.	Pts	N/R	Features	Study-drug (DMARDs/GC)	Follow-up	Outcome
Specks (235)	1 WG	R	CNS, ENT	RTX (-/+)	14 ms	CR
Cheung (236)	1 WG	R	Scleritis	RTX (+/+)	7 ms	Responder
Freidlin (237)	1 WG	R	Scleritis + PUK	RTX (-/+)	3 ms	CR
Kowalewska (238)	1 WG	R	L, ENT; IFX failure	RTX (+/+)	2 ys	CR
Ferraro (239)	1 WG	R	L, ENT; IFX failure; CHOP for abdominal NHL	RTX (+/+)	10 ms	CR
Henes (56)	6 WG	R	ENT, K, SNC	RTX (-/+)	16 ms	4CR,1PR, 1 relapse
Roccatello (240)	4 MPA, 2 WG, 1 CSS	R	Necrotising GNF, PNS	RTX (+/+)	12 ms	7/7CR
Kaushik (241)	1 CSS	R	K, L, S	RTX (+/+)	3 ms	CR
Koukoulaki (242)	2 CSS	R	ENT, PNS, L, C; ENT, PNS	RTX (+/+)	10 ms	CR
Ribeiro (243)	1 PAN	R	Skin, PNS	RTX (+/+)	2 ys	CR
Sonomoto (244)	1 PAN	R	Skin, PNS	RTX (+/+)	n.s.	CR

WG: Wegener's granulomatosis; MPA: microscopic polyangiitis; CSS: Churg-Strauss syndrome; CNS: central nervous system; PNS: peripheral nervous system; PUK: peripheral ulcerative keratitis; ENT: ear-nose-throat involvement; GNF: glomerulonephritis; K: kidney involvement; L: lung involvement; C: cardiac involvement; CR: complete response; PR: partial response; PAN: polyarteritis nodosa; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; IFX: infliximab; n.s.: not specified.

Clinical relapses following RTX therapy in AAV patients are frequent (up to 50-60% of patients) with a median relapse time ranging between 12 and 18 months, but re-treatment is often effective and safe (19, 55, 60, 65, 66).

Successful persistent clinical remission has been reported in 8 patients pre-emptively treated with RTX for isolated ANCA titers' increase without clinical relapse. It should be noted, however, that increased ANCA titers do not necessarily predict clinical recurrences (61, 65).

On the basis of these data, we formulated the following recommendations:

- Rituximab can be used to induce disease remission in association with glucocorticoids in patients with ANCA-associated vasculitis in alternative to cyclophosphamide (level of evidence Ib, strength of recommendation A).
- There is insufficient evidence to recommend the use of rituximab in patients with severe alveolar haemorrhage or severe renal failure. However, rituximab may be used in patients that fail cyclophosphamide therapy (level of evidence IV, strength of recommendation C).
- Patients with refractory granuloma-

tous manifestations, especially retro-orbital granulomata, may respond less well to rituximab (level of evidence IV, strength of recommendation C).

- In case of clinical relapse, re-treatment with the same initial rituximab schedule, with or without concomitant disease-modifying anti-rheumatic drugs and oral GC, should be considered (level of evidence IIa, strength of recommendation C).
- We do not endorse pre-emptive RTX therapy for isolated ANCA titers' increase in the absence of a clinical flare (level of evidence IV, strength of recommendation C).

b) Anti-TNF- α agents off-label therapy

The only available RCT, the WGET (Wegener's Granulomatosis Etanercept trial), randomised 180 patients with active Wegener granulomatosis (BVAS/WG>3) to receive either twice weekly subcutaneous etanercept (25 mg) or placebo (67). Patients with severe disease received CYC and GC at enrolment and those with limited disease methotrexate and GC at enrolment. Once the disease was controlled, the doses of the standard medications were

tapered according to a predefined protocol. Severe flares were treated with CYC and GC, while limited flares were treated with increases in the dose of methotrexate, prednisone, or both. The primary outcome measure was sustained disease remission, defined as a BVAS/WG of 0 for at least six months. Secondary outcome measures included the number and rate of flares during the treatment phase, the percentage of patients with a sustained low level of disease activity (defined by a BVAS/WG <3 for at least six months), the percentage of patients with remission (defined by a BVAS/WG of 0), and AE. The percentage of patients meeting the primary end point did not differ between the etanercept and the placebo-treated arm (69.7% vs 75.3%). Likewise, etanercept did not prove superior to placebo in meeting secondary outcomes.

Life-threatening and serious AE were similarly high in both groups, but six solid cancers occurred in the etanercept group *versus* none in the placebo arm, suggesting a significant higher risk of solid malignancy that might be related to combined TNF- α inhibition and CYC.

In summary, despite encouraging results of an early study, the WGET suggested that etanercept was not effective in AAV and in particular did not prevent relapses more than did placebo (68). In addition, there was a higher incidence of solid tumours in the etanercept group.

In a large open-label trial on AAV patients, eligible patients were entered into one of two studies (69). Study I examined patients with acute flares of AAV that were not immediately life-threatening (BVAS ≥ 10), while study II examined patients with active AAV (BVAS ≥ 4) that had received at least 3 months of combination therapy with prednisolone and immunosuppressive agents without achieving remission. Patients in both study subgroups initially received infliximab (5 mg/kg) intravenously at 0, 2, 6, and 10 weeks. Study II patients achieving remission were invited to continue receiving infliximab at six weekly intervals for 1 year. Concomitant therapy in study I was oral CYC (2 mg/kg per day) for 14 weeks and a reducing course of oral prednisolone. Pa-

tients in remission were then switched to a remission maintenance regimen of prednisone and azathioprine 2 mg/kg or mycophenolate mofetil if azathioprine was contraindicated. Twenty-eight patients (88%, 14 in each study) achieved remission (BVAS ≤ 1) at a mean time of 6.4 weeks. GC requirement decreased in both groups. Of the 28 patients achieving remission, 5 (18%) experienced relapse of disease requiring a change in medication. Seven serious infections were recorded. The results of this study are consistent with efficacy of infliximab in active AAV. Globally, other open-label trials and case series related to the use of infliximab in active refractory AAV have shown an overall rate of clinical response of 80%, mostly sustained for at least 6 months (70-72). The majority of AAV patients had Wegener's granulomatosis (69, 71, 73-76). Encouraging results of infliximab therapy have been described in refractory granulomatous manifestations of AAV. In a small case series, infliximab added to standard therapy (including intravenous CYC and oral GC) prevented blindness due to refractory progressive retro-orbital granulomas in all patients (3/3), improving ocular motility and symptoms and reducing ocular lesions on MRI images. Remission was also achieved in 6 patients with rapidly progressive glomerulonephritis and cavitating pulmonary nodules (70). Successful treatment with infliximab of refractory meningeal and ocular involvement was also reported in 2 Wegener granulomatosis patients (77, 78).

On the basis of these data, we formulated the following recommendations:

- We do not recommend the use of anti-TNF- α agents in patients with ANCA-associated vasculitis that have attained drug-induced remission to prevent flares upon tapering glucocorticoids and immunosuppressants (level of evidence Ib, strength of recommendation A).
- Anti-TNF- α agents might be used in selected refractory patients with ANCA-associated vasculitis as adjunctive therapy to standard ongoing immunosuppressive medications (level of evidence IV, strength of recommendation C).

Polyarteritis nodosa

There are only two reported patients with refractory polyarteritis nodosa (PAN) treated with RTX. In both patients, RTX led to complete resolution of cutaneous ulcers, unresponsive to previous conventional immunosuppressive drugs (Table V). Three case reports also described successful treatment with infliximab infusions (5 mg/kg), with amelioration of skin and peripheral nervous system manifestations, and of aneurysm changes in two and in one patient, respectively (Table VI).

On the basis of these data, we formulated the following recommendations:

- Rituximab might be considered in association with immunosuppressive drugs for refractory polyarteritis nodosa (level of evidence IV, strength of recommendation D).
- Infliximab might be considered in association with immunosuppressive drugs for refractory polyarteritis nodosa (level of evidence IV, strength of recommendation D).

Sjögren's syndrome

a) Rituximab off-label therapy

A RCT showed some beneficial effects of RTX in patients with primary Sjögren's syndrome (pSS) on fatigue and joint pain, while objective improvement in salivary and lacrimal glandular function tests was less impressive (79). The only significant difference reported between the two treatment groups (RTX arm: 1000 mg at 0 and 2 weeks, in association with DMARDs and high-dose oral GC; placebo arm: placebo plus DMARDs and GC), resided in VAS pain and quality of life assessment at 6 months of follow-up.

The effect of RTX on sicca features was also analysed in three other studies (2 retrospective analyses and one open-label trial) with conflicting results (57, 80, 81). With regard to the effect of RTX in pSS-related extra-glandular manifestations, amelioration of systemic features like cryoglobulinemia (57, 81), pulmonary involvement (83), severe cytopenias (81), synovitis, and mononeuritis (14, 57, 81) has been reported.

Studies of RTX in pSS including patients with pSS-related lymphoma

showed an overall successful response in 8 out of 13 of treated patients (57, 80, 81). Better results have been reported for combined therapy RTX-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) *versus* CHOP alone in pSS patients affected by aggressive diffuse large B-cell lymphoma (82). Other case reports (Table VI) showed a good efficacy and safety profile of RTX in pSS-associated maltoma. When reported, incisional biopsies of the parotid gland before and after RTX treatment showed improvement of histopathological characteristics of SS, especially for B and T lymphocytic infiltration, with possible regeneration of salivary gland tissue, especially in early disease (83). Re-treatment with RTX has been reported in a few patients with pSS apparently with results comparable to the first treatment course (84). Heterogeneity in classification criteria and outcome measures as well as use of concomitant medications make difficult to arrive at definite conclusions on the role of RTX in pSS.

On the basis of these data, we formulated the following recommendations:

- Rituximab is not recommended for the treatment of sicca syndrome manifestations in patients with primary Sjögren's syndrome (level of evidence Ib, strength of recommendation A).
- Rituximab might be used for refractory extra-glandular manifestations associated with primary Sjögren's syndrome, including articular, peripheral nerve system, cutaneous, pulmonary, and renal manifestations (level of evidence IV, strength of recommendation D).
- Rituximab can be used to treat primary Sjögren's syndrome-associated lymphoma (level of evidence IIa, strength of recommendation C).

b) Anti-TNF- α agents off-label therapy

Two RCTs have investigated the use of infliximab and etanercept, respectively, in pSS.

In the RCT of Remicade in pSS (TRIPSS), 103 patients were randomly assigned to receive infliximab infusions (3 doses of 5 mg/kg each at

Table VI. AAV-related case reports and series with off-label anti-TNF agents.

Ref.	Pts	N/R	Features	Study-drug (DMARDs/GC)	Follow-up	Outcome
Sangle (245)	1 CSS	R	n.s.	Infliximab (+/+)	6 ms	F
Tiliakos (246)	1 CSS	R	J, Skin, E	Infliximab (+/+)	n.s.	CR
Aries (247)	1 CSS/RA	R	J	Infliximab>etanercept (due to infusion reaction) (n.s)	n.s. (abs)	CR
Arbach (248)	3 CSS	R	C, CNS	2 Infliximab;1 etanercept	1 ys	1 CR, 2 PR
El-Shabrawi (249)	1 WG	R	E	Infliximab (+/+)	8 ms	CR
Hermann (250)	1 WG	R	CNS	Infliximab (+/+)	12 ms	CR
Wu (251)	1 PAN	R	K aneurysmal haemorrhage	Infliximab (+/+)	40 ds	CR
Al-Bishri (252)	1 PAN	R	Skin, PNS	Infliximab (+/+)	4 ys	CR
Garcia-Porrua (253)	1 PAN/uSpA	R	Skin	Infliximab (+/+)	18 ms	CR

J: joint involvement; CNS: central nervous system; PNS: peripheral nervous system; ENT: ear-nose-throat; GNF: glomerulonephritis; K: kidney involvement; L: lung involvement; C: cardiac involvement; uSpA: undifferentiated spondyloarthritis; F: failure; E: ear involvement; CSS: Churg-Strauss syndrome; WG: Wegener's granulomatosis; CR: complete response; PR: partial response; n.s.: not specified; ms: months; ds: days; ys: years.

baseline, 2 and 6 weeks) or placebo (85). No immunosuppressive treatment was allowed except for hydroxychloroquine (HCQ) and low-dose GC in each arm. Follow-up duration was 22 weeks. Infliximab therapy conferred no significant improvement over placebo in subjective or objective outcome measures of glandular and extra-glandular involvement.

In contrast, a small uncontrolled open-label trial showed a significant reduction in fatigue, joint pain and sicca symptoms and signs just at 2 weeks and lasting up to 14 weeks in infliximab treated patients (3 doses of 3 mg/kg at baseline, 2 and 6 weeks) without background immunosuppressive treatment (86). The discrepancies between these two studies might be explained by their different design, different inclusion criteria, drug dosage and comedications.

In the RCT on etanercept in pSS, patients with active disease according to laboratory findings (increased baseline levels of ESR and/or immunoglobulin G) received etanercept at a dosage of 25 mg twice weekly for 12 weeks or placebo (87). Apart from a modest decrease in ESR levels in the etanercept group, there were no significant between-group differences in subjective measures of oral or ocular symptoms, immunoglobulin G levels, Schirmer test results, or salivary gland flow. On the same line, in another open study

12-week treatment of etanercept 25 mg twice weekly did not appear to reduce sicca symptoms and signs in pSS (88). On the basis of these data, we formulated the following recommendations:

- Anti-TNF agents (infliximab and etanercept) are not recommended for primary Sjögren's syndrome because of lack of clinical efficacy (level of evidence Ib, strength of recommendation A).
- Adalimumab can not be recommended in Sjögren's syndrome because of lack of evidence.

Systemic sclerosis

a) Rituximab off-label therapy

In a RCT, 14 anti-Scl-70 positive patients with diffuse systemic sclerosis (SSc) with associated interstitial lung disease diagnosed with high-resolution computerised tomography of the chest (HRCT) and/or pulmonary functional tests were randomised to receive or not two cycles of RTX (4 weekly infusions at 375 mg/m² dosage) at baseline and after 24 weeks in association with any ongoing immunosuppressive treatment (89). At the end of the follow-up in the active arm a significant improvement was observed in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) in contrast with their deterioration in placebo group, along with a stability of radiological assessment on lung HRCT

scan *versus* a minor deterioration in the control arm. In the isolated analysis, skin thickening, assessed with the Modified Rodnan Skin Score (mRSS) improved significantly more in RTX group compared with baseline score, while no substantial amelioration was noted in the control group (90).

Further data derive from two open-label trials reporting on the use of a single course of RTX in SSc patients, a proportion of whom had mild lung involvement. In a study on 8 patients with diffuse SSc RTX (1000 mg at baseline and at day 15), together with iv GC premedication, low-dose DMARDs and low-dose GC significantly improved the mRSS at 24 week, while parameters of lung disease remained stable (91). In another study, 15 patients with early onset (<18 months), rapidly progressive SSc were treated with the same RTX schedule and low-dose GC (92). RTX treatment resulted in depletion of both circulating and dermal B cells but had no significant effect on skin disease at 6 months of follow up. However no progression of major organ involvement was noticed in such a population. Patients with severely compromised lung and heart function were excluded from both above studies.

On the basis of these data, we formulated the following recommendations:

- Rituximab may be used as adjunctive treatment to ongoing immunosuppressants to treat refractory interstitial lung disease in patients with diffuse systemic sclerosis (level of evidence Ib, strength of recommendation A).
- Rituximab is not be recommended to treat cutaneous involvement in systemic sclerosis (level of evidence IIb, strength of recommendation C).

b) Anti-TNF-α agents off-label therapy

There is a retrospective analysis of 18 patients with limited SSc-associated, refractory arthritis treated with etanercept (25 mg twice weekly or 50 mg once weekly) in combination with DMARDs (mostly MTX) and prednisone 5 mg daily (93). A significant subjective and objective improvement was reported in joint involvement at the

Table VII. Sjögren’s syndrome and pSS related MALTOMA case reports.

Ref.	Pts	N/R	Features	Study drug (other drugs)	Follow-up	Outcome
Ahmadi-Simab (254)	1	R	Anterior scleritis	RTX (+/+)	6 ms	Responder
Touma (255)	1	R	K (GN)	RTX (-/-)	n.s.	Responder
Ring (256)	1	R	K (RTA)	RTX (-/-)	1 ys	F
Somer (257)	1	N	pSS maltoma	RTX (-/-)	1 ys	CR
Pijpe (258)	1	N	pSS maltoma	RTX (-/-)	6 ms	CR

K: kidney; GN: glomerulonephritis; RTA: renal tubular acidosis; CR: complete response; R: refractory case; F: failure; N: new case.

latest follow-up at a mean of 30 months later. In contrast, in a prospective open-label trial infliximab infusions without DMARDs and GC provided no significant benefit on skin disease in a cohort of 16 patients with rapidly progressive cutaneous involvement (94). In a case series of 4 patients with erosive polyarthritis associated with systemic sclerosis treated with TNF-α inhibitors, three out of four patients had significant joint improvement (95). Furthermore, in all the patients mRSS improved by more than 35%, flexion contractures decreased in 2 patients and digital ulcers improved in other two. Other uncontrolled observations suggest some efficacy of TNF-α blockade for skin disease (96), unclear efficacy (97), and benefit for lung disease (98).

On the basis of these data, we formulated the following recommendations:

- TNF-α inhibitors are not recommended to treat systemic sclerosis because of limited data. However, they may be considered in patients with systemic sclerosis and refractory erosive arthritis (level of evidence IV, strength of recommendation C).

Idiopathic myositis

a) Rituximab off-label therapy

Case reports (Table VIII), case series

(99-101), and open-label trials (102, 103) suggest noteworthy efficacy of RTX in resistant dermatomyositis (DM), polymyositis (PM), and the anti-synthetase syndrome.

In an open-label trial, 6 out of 7 DM patients exhibited major clinical and laboratory responses with early and significant (>12%) improvement in muscle strength and benefit on cutaneous and pulmonary involvement (102). In contrast, in another study, RTX displayed less marked efficacy on muscle and skin manifestations in 8 DM patients (103).

Small pilot studies, case reports and series have claimed efficacy of RTX in about 20 patients with refractory anti-synthetase syndrome, sometimes with associated interstitial lung disease (57, 102, 104-107). RTX increased muscle strength, normalised serum creatine kinase (CK) levels, and led to regression of ground glass pulmonary lesions on HRCT scales. Most relapsing patients with an established diagnosis of myositis promptly responded to re-treatment (105). Treatment-related AE have infrequently been reported (103, 107, 108). On the basis of these data, we formulated the following recommendations:

- Rituximab treatment may be considered in patients with refractory idio-

Table VIII. SSc case reports on RTX off-label use.

Ref.	Pts	N/R	Features	Study drug (other drugs)	Follow-up	Outcome
Gottenberg (57)	1	R	Severe SSc	RTX (+/+)	5 ms	F
McGonagle (259)	1	R	ILD	RTX (+/+)	2 ys	PR
Fabri (260)	1	R	M	RTX (+/+)	11	CR

ILD: interstitial lung disease; M: myositis; R: refractory case; F: failure; CR: complete remission; PR: partial remission; ms: months; ys: years..

pathic myositis patients that have failed glucocorticoids and standard immunosuppressive therapy (level of evidence IV, strength of recommendation C).

- Rituximab treatment might be considered in patients with refractory anti-synthetase syndrome that have failed glucocorticoids and standard immunosuppressive therapy (level of evidence IV, strength of recommendation C).

b) Anti-TNF- α agents off-label therapy

Few open-label trials, one retrospective analysis, case series and case reports have shown no significant clear positive effects of anti-TNF- α agents (infliximab, etanercept) in both refractory longstanding disease and in drug-naïve early-onset disease. Worsening of clinical manifestations has also been described mainly in DM (109-114). Improvement was mainly noted in extramuscular non-cutaneous features (112-115). A limited number of case may suggest some benefit of infliximab (116-119). No data are available for adalimumab therapy in idiopathic myositis. On the basis of these data, we formulated the following recommendations:

- TNF- α inhibitors are not recommended to treat idiopathic myositis (level of evidence IV, strength of recommendation C).

c) Anakinra off-label therapy

There is only a case report of anti-synthetase syndrome with refractory polyarthritis that responded to anakinra (120).

On the basis of the available data, we formulated the following recommendations:

- Anakinra can not be recommended to treat idiopathic myositis due to insufficient evidence.

Inclusion body myositis

Few data are available on anti-TNF- α treatment in patients with inclusion body myositis (IBM). In one study, infliximab in association with DMARDs and GC appeared to stabilise disease progression at short-medium follow-up (112), while in a small group of patients

Table IX. Idiopathic myositis case reports and series on RTX off-label use.

Ref.	Pts	N/R	Features	Study drug (DMARDs/GC)	Follow-up	Outcome
Vanderbroucke (261)	1	R	RF, antiJo1+	RTX (+/+)	3 ms	PR
Touma (262)	1	R	HD	RTX (-/+)	8 ms	CR
Tournadre (263)	1	R	Anti-Jo1+, Pem	RTX (+/+)	15 ms	CR
Majmudar (264)	3	R	2 DM, 1 PM	RTX (+/+)	3 ms	CR
Arlet (265)	2	R	Anti-SRP	RTX (+/+)	5 ws	2/2 CR

RF: respiratory failure; HD: heart disease; Pem: pemphigus; PR: partial response; CR: complete response; anti-Jo1: anti-histidyl-tRNA synthetase antibodies; anti-SRP: anti-signal recognition particle antibodies; DM: dermatomyositis; PM: polymyositis; ms: months; ws: weeks.

(18) etanercept resulted slightly more efficacious in improving handgrip at 12 months compared with control group (121). However, the effects may well be due to the natural fluctuations of IBM progression and can not reliably be attributed to anti-TNF- α therapy.

On the basis of the available data, we formulated the following recommendations:

- Anti-TNF- α agents can not be recommended to treat inclusion body myositis due to insufficient evidence of efficacy.

Polymyalgia rheumatica

Anti-TNF- α agents off-label therapy

Infliximab did not prove more effective than placebo in a RCT involving newly-diagnosed PMR patients (122). 52 patients with newly diagnosed isolated PMR received prednisone 15 mg/day tapered off in sixteen weeks in the absence of flares. Infusions of placebo or infliximab (3 mg/kg) were given at 0, 2, 6, 14, and 22 weeks. The primary study outcomes were the numbers of relapse/recurrence free patients, while secondary outcomes included the number of patients no longer taking prednisone, the number of flares, the duration of prednisone therapy, and the cumulative prednisone dose throughout the planned trial duration of 52 weeks. The results of this study showed no significant effect of infliximab on any of the outcome variables at week 22 and 52.

In contrast, data from open-label trials and case series have shown that both infliximab and etanercept might act as steroid-sparing agents in patients with longstanding refractory disease (123-125). In addition, a brief course of infliximab infusions (3 mg/kg at baseline, 2, 6, 14 weeks) was successfully used as induction therapy in 7 PMR patients with comorbidities absolutely contraindicating GC treatment, with achievement of long-term remission (126).

On the basis of these data, we formulated the following recommendations:

- TNF- α inhibitors are not recommended as adjunctive therapy to GC to treat newly diagnosed polymyalgia rheumatica patients because of evidence of lack of additional efficacy over and above that provided by GC alone in this subset of patients (level of evidence Ib, strength of recommendation A).
- TNF- α inhibitors may be considered in patients with longstanding polymyalgia rheumatica refractory to low-dose (<7.5 mg/day) glucocorticoids (level of evidence IV, strength of recommendation C).

Sarcoidosis

a) Anti-TNF- α agents off-label therapy

A RCT on 128 patients showed that add-on infliximab (3–5 mg/kg at baseline, then at 2, 6, 12, 18, and 24 weeks) to standard ongoing DMARDs and GC therapy resulted in a significant improvement over placebo in the mean change of the percent predicted FVC from baseline to week 24 (+2.5%) in patients with non-severe lung sarcoidosis (127). However, this improvement was not sustained after therapy cessation in the subsequent 6 weeks of observation, while symptoms did not appear to significantly improve. Improvement in chest radiographic lung lesions and in serum angiotensin converting enzyme (ACE) levels was noticed in the

Table X. Sarcoidosis case reports and series on off-label biologic therapies.

Ref.	Pts	N/R	Features	Study drug (other drugs)	Follow-up	Outcome
Katz (266)	1	R	Papilloedema,	Infliximab (+/+)	13 ms	CR
Pritchard (267)	5	R	Optic atrophy Ocular granulomatous uveitis; neurological, L	Infliximab (+/+)	6 ms	4 CR, 1 PR
Santos (268)	4	R	Neurological	Infliximab (+/+)	20 ms	4/4 CR
Sodhi (269)	4	R	Neurological	Infliximab (+/+)		4/4 Responder
Sollberger (270)	1	R	Neurological	Infliximab (+/+)	7 ms	CR
Guilpain (271)	1	R	Neurological	Infliximab (+/+)	2 ms	F
Pettersen (272)	1		Neurological	Infliximab	n.s.	Responder
Carter (273)	1	R	Neurological	Infliximab (+/+)	5 ms	CR
Doty (274)	6	R	Skin	Infliximab (+/+)	1 ys	6/6 CR
Heffernan (275)	1	R	Skin	Infliximab (+/+)	6 ws	CR
Haley (276)	1	R	Skin	Infliximab (+/+)	12 ws	CR
Sweiss (277)	6	R	Skin, Eye	Infliximab (+/+)	4-19 ms	3/3CR (skin) 3/3CR (eye)
Mallbris (278)	1	R	Skin	Infliximab (+/+)	14 ws	CR
Meyerle (279)	1	R	Skin	Infliximab (+/+)	12 ws	CR
Ahmed (280)	1	R	kidney	Infliximab	n.s.	Responder
Yee (281)	1	R	Enteropathy, myopathy	Infliximab (+/+)	100 ds	CR
Agrawal (282)	1	R	Sarcoid sacroiliitis	Infliximab	n.s.	Responder
Menon (283)	1	R	Sarcoid-Hypercalcemia INF-alpha-induced	Infliximab (-/+)	3 ms	CR
Tuchinda (284)	1	R	Skin	Etanercept (-/-)	n.s.	CR
Khanna (285)	1	R	Skin	Etanercept (+/+)	18 ms	CR
Hobbs (286)	1	R	Arthritis	Intrarticular Etanercept (-/-)	9 ms	CR
Philips (287)	1	R	Skin	Adalimumab (+/+)	9 ws	CR
Heffernan (288)	1	R	Skin	Adalimumab (+/-)	10 ws	CR
Callejas-Rubio (289)	1	R	Multiorgan	Adalimumab	n.s.	CR
Gottenberg (57)	1	R	L	RTX (+/+)	11 ms	CR
Belkhou (290)	1	R	L, J	RTX (+/+)	1 ys	CR

R: refractory case; L: lung involvement; J: joint involvement; CR: complete response; PR: partial response; F: failure; ms: months; ws: weeks; ds: days; ys: years; n.s.: not specified.

active treatment group *versus* placebo, but these results were quite similar to those previously reported in sarcoidosis on GC medication alone (128, 129). A post-hoc analysis revealed a trend for some benefit of TNF- α blockade on extrapulmonary features (130). A high frequency of clinical relapses after anti-TNF- α treatment cessation has been reported (131, 132). Another study showed that etanercept (25 mg/week) benefited pulmonary involvement in 5 of 17 treated patients (133). There is a RCT testing the effect of etanercept *versus* placebo in different types of refractory ocular involvement due to sarcoidosis (anterior

uveitis in 9 patients, posterior uveitis in 5 patients and pars planitis in 9). No significant between-group differences in ocular response after 6 months of therapy were noticed (134). Data for infliximab use will be presented herein elsewhere (135-136). For other organ involvement in sarcoidosis only data from case series and reports are available (Table X). On the basis of these data, we formulated the following recommendations:
– There is insufficient evidence of clinically relevant efficacy to recommend the use of TNF- α inhibitors to treat lung involvement due to sarcoidosis refractory to standard treat-

ment (level of evidence Ib, strength of recommendation A).

- Etanercept is not recommended to treat refractory ocular sarcoid involvement due to lack of efficacy (level of evidence 1b, strength of recommendation A).
- Infliximab might be considered to treat refractory sarcoid-related inflammatory eye disease as adjunctive therapy (level of evidence IV, strength of recommendation C).
- TNF- α inhibitors may be considered to treat severe, refractory cutaneous disease due to sarcoidosis (level of evidence IV, strength of recommendation D).
- In refractory neurosarcoidosis infliximab may be considered (level of evidence IV, strength of recommendation D).

b) Rituximab off-label therapy

Add-on RTX has shown some benefit in two cases with mesenteric and cervical lymphadenopathy and with lung and articular involvement, respectively (Table X).

- Rituximab can not be recommended to treat sarcoidosis due to insufficient evidence.

Adult-onset Still’s disease

a) Anti-TNF- α agents off-label therapy

Data on patients with adult-onset Still’s disease (AOSD) treated with infliximab (usually 3 mg/kg) derive from prospective and retrospective case series and reports (137-143). Most cases had refractory disease. Clinical and laboratory responses were often rapid but often partial and temporary, requiring repeated therapy. Etanercept has shown efficacy in terms of arthritis and to a lesser extent of systemic features (143-146). In a case series of 20 patients treated with TNF- α inhibitors, 16 had a partial response and most patients stopped therapy after one year usually because of clinical inefficacy. Resolution with etanercept of nephrotic syndrome due to renal AA amyloidosis in AOSD has also been reported (147). On the basis of these data, we formulated the following recommendations:
– TNF- α inhibitors might be consid-

ered as adjunctive therapy in refractory Still's disease (level of evidence IV, strength of recommendation C).

b) Anakinra off-label therapy

Data on patients with (often refractory) AOSD treated with anakinra come from open-label trials and case series (148-156). Anakinra 100 mg daily in association with DMARDs (especially MTX) and GC usually resulted in rapid and sustained clinical and laboratory improvement and GC dose sparing.

In the largest case series including also pediatric patients, following treatment with Anakinra 11 out of 15 patients achieved a $\geq 50\%$ improvement, while GC could be tapered (148). Anakinra resulted anecdotally effective in a case of life-threatening AOSD (150). However, a case of Systemic Inflammatory Response Syndrome and Adult Respiratory Distress Syndrome in a young adult-onset Still's disease patient, occurring 10 days after the introduction of anakinra has been reported (157).

On the basis of these data, we formulated the following recommendations:

- Anakinra can be recommended to treat refractory Still's disease (level of evidence IV, strength of recommendation C).

c) Rituximab off-label therapy

Three cases have been reported on the use of RTX in refractory AOSD. Clinical efficacy was noted in two of them (57, 158).

- Rituximab can not be recommended for refractory Still's disease because of insufficient evidence of efficacy (level of evidence IV, strength of recommendation D).

Relapsing polychondritis

a) Rituximab off-label therapy

A retrospective trial tested different therapeutic regimens of anti-CD20 therapy in addition to ongoing immunosuppressive therapies in 9 relapsing polychondritis (RP) patients (159). No cases of complete clinical remission were observed at short-medium follow-up.

On the basis of these data, we formulated the following recommendations:

- Rituximab is not recommended to treat refractory relapsing polychon-

dritis because of lack of sufficient evidence (level of evidence IV, strength of recommendation D).

b) Anti-TNF- α agents off-label therapy

Rapid and sustained clinical efficacy of infliximab (3 mg/kg at baseline, 2, 6 and then every 8 weeks) has been reported in active refractory diffuse anterior scleritis associated with RP, together with persistent benefits on joint and laryngotracheal symptoms (160).

Two further cases of refractory disease showed sustained clinical and biological response after 8 infliximab infusions (5 mg/kg at 0, 2, 6, then every 8 weeks). GC could be tapered and there were no further clinical relapses (161). Prompt resolution of severe laryngotracheal involvement has also been reported (162).

Two cases have described the clinical efficacy of etanercept (25 mg subcutaneously twice weekly) in RP, for polyarthritis, auricular and nasal chondritis and trigeminal neuralgia in one patient and in severe infliximab-refractory tracheomalacia, respectively (163, 164).

On the basis of these data, we formulated the following recommendations:

- Infliximab might be considered to treat refractory relapsing polychondritis (level of evidence IV, strength of recommendation D).

c) Anakinra off-label therapy

Prompt and sustained clinical and laboratory responses have been observed in 2 refractory RP patients with daily subcutaneous 100 mg anakinra injections, even after failure of anti-TNF treatment. Discontinuation of GC medication was also achieved without side effects (165, 166).

On the basis of these data, we formulated the following recommendations:

- Anakinra can not be recommended to treat relapsing polychondritis due to insufficient evidence (level of evidence IV, strength of recommendation D).

Inflammatory eye diseases

a) Seronegative spondyloarthropathies and HLA B27 associated uveitis

In a meta-analysis by Braun *et al.* involving 717 ankylosing spondylitis (AS)

patients, both infliximab and etanercept proved effective in significantly decreasing the number of anterior uveitis (AU) flares (167). The frequencies of AU relapses in the placebo group was 15.6 per 100 patients-years compared to a mean of 6.8 flares up per 100 patients-years in those subjects receiving anti-TNF agents ($p=0.01$). This reduction was slightly more marked for infliximab over etanercept but the difference between them was not significant.

Data from another recent meta-analysis showed that uveitis flares rate in AS patients treated with etanercept (mostly at the dosage of 25 mg s.c. bi-weekly) was significantly lower than the one reported among subjects treated with placebo in 4 placebo-controlled trials (8.6 and 19.3 per 100 subject years, respectively; $p=0.03$), while uveitis events were similar for etanercept (50 mg s.c. weekly) and sulfasalazine (≤ 3 g/die) in a single active-comparator trial (10.7 and 14.7 per 100 subject years, respectively; $p=0.49$)(168). Thus, etanercept seems not to have efficacy on uveitis superior to that of sulfasalazine (169). On a similar line, in a RCT involving 20 patients with chronic or recurrent non-infectious ocular inflammation associated or not with autoimmune systemic diseases (idiopathic, HLA-B27 associated, RA- and SLE-related) etanercept was not superior to placebo in preventing ocular relapse on DMARD tapering (170).

In a small prospective series, 7 patients with acute flares of HLA-B27 positive anterior uveitis were treated with a single infliximab infusion of 10 mg/kg with an immediate improvement in ocular symptoms and signs. However, 5 patients experienced a recurrence of disease suggesting that a single infliximab infusion might be effective only in the short term (171).

A retrospective observational analysis conducted in 266 spondyloarthropathy patients showed that anti-TNF- α antibodies (infliximab and adalimumab) significantly decreased the number of ocular flares, whereas the soluble TNF receptor (etanercept) did not (172). Likewise, in a subanalysis of an open-label trial containing 1250 patients with longstanding active AS, adalimumab

(40 mg every other week) decreased the rates of anterior uveitis flares (173).

These results suggest superiority of monoclonal anti-TNF- α antibodies over etanercept in controlling ocular inflammation in spondyloarthritis. Other cases suggest benefit of infliximab for ocular disease (174, 176).

b) Psoriatic ocular involvement

Fewer data are available regarding the efficacy of anti-TNF- α agents to treat psoriatic ocular inflammatory disease. They include the following cases: 5 panuveitis (4 treated with infliximab, 1 with adalimumab), 3 AU (2 treated with infliximab, 1 with adalimumab), and 3 scleritis (2 treated with infliximab, 1 with adalimumab) (174-177). Anti-TNF- α agents were used for refractory inflammatory eye disease. All patients achieved complete ocular control with only one patient with AU flaring on infliximab therapy (174). However, a patient has been reported that developed for the first time an acute anterior uveitis 7 months after the initiation of etanercept (175).

On the basis of these data, we formulated the following recommendations:

- Infliximab and etanercept may be considered to treat refractory anterior uveitis flares in patients with ankylosing spondylitis (level of evidence Ia, strength of recommendation A). Anti-TNF- α antibodies (infliximab, adalimumab) appear to have superior efficacy compared to that of etanercept in controlling eye inflammation in patients with spondyloarthritis (level of evidence IIb, strength of recommendation B).
- Infliximab and adalimumab may be considered for refractory psoriatic inflammatory eye involvement (panuveitis, anterior uveitis, scleritis) (level of evidence IV, strength of recommendation C).

c) RA ocular involvement

Regarding ocular involvement in RA patients treated with anti-TNF- α agents, the following cases have been reported: 6 scleritis (3 treated with etanercept with complete response, 3 with infliximab at 3/5 mg/kg with 1 complete and 1 partial response), 1 panuveitis (PAU) success-

fully treated with continuous infliximab infusions at 5 mg/kg every 8 weeks in association with MTX and GC and one single case of severe scleritis associated with sight-threatening peripheral ulcerative keratitis that responded to infliximab (174, 175, 178, 179).

At the same time, various new cases of ocular disease in RA patients treated with etanercept have been described (175, 178). On the other hand, etanercept revealed efficacy in a patient affected by PAU-associated cystoid macular oedema within 4 months after the onset of treatment (180). In the only RA patient with uveitis included in a RCT, etanercept did not succeed in preventing ocular flares (170).

On the basis of these data, we formulated the following recommendations:

- Infliximab may be considered as adjunctive therapy to treat refractory ocular involvement, especially scleritis, in rheumatoid arthritis (level of evidence 4, strength of recommendation C).
- Etanercept is not recommended to treat refractory ocular disease associated with rheumatoid arthritis (level of evidence IV, strength of recommendation D).

d) Sarcoidosis ocular involvement

In a RCT etanercept did not show any advantages over placebo at 6 months of observation in different types of refractory sarcoid ocular involvement (AU in 9 patients, posterior uveitis in 5 patients and pars planitis in 9) (134). Further data on this topic derive from patients included in heterogeneous cohorts of prospective open-label trials and of one retrospective analysis (135, 136, 169, 175, 178, 181). Globally, 5 patients with refractory panuveitis were successfully treated with infliximab mainly in association to ongoing DMARD and GC therapy. Successful treatment of refractory retinal vasculitis with infliximab has also been described (170). Finally, adalimumab proved effective in a case of multiresistant sarcoid PAU with sustained benefit (183).

On a note of caution, physicians should keep in mind that sarcoid-like ocular lesions might develop during anti-TNF- α therapy (184, 185).

On the basis of these data, we formulated the following recommendations:

- Etanercept can not be recommended for refractory ocular sarcoid involvement due to lack of efficacy (level of evidence 1b, strength of recommendation A).
- Infliximab might be considered for treating refractory ocular sarcoid involvement as adjunctive therapy (level of evidence IV, strength of recommendation C).
- Adalimumab can not be recommended for refractory ocular sarcoid involvement due to insufficient evidence (level of evidence IV, strength of recommendation D).

Gout and Pseudogout

An open-label study was performed involving 10 patients with recalcitrant attacks of acute arthritis due to chronic gout resistant or intolerant to previous standard therapies (186). All patients rapidly responded to three daily 100 mg subcutaneous anakinra injections in association with low-dose oral GC. A further case report described marked subjective and objective amelioration of articular inflammation at 12 weeks after a brief course (3 days) of s.c. anakinra injections (100 mg daily) in association with low-dose oral GC (187).

A case of successful treatment with daily s.c. 100 mg anakinra in a resistant pseudogout patient has also been described. The patient showed a complete clinical and laboratory response within 2 weeks from treatment onset with sustained benefit at 6 months of follow-up (188).

From these available data we could suggest the following recommendation:

- Anakinra is not recommended to treat refractory gout or pseudogout because of insufficient evidence of long-term benefit (level of evidence IV, strength of recommendation D).

Ankylosing spondylitis

A pilot study conducted in 9 active, refractory patients with AS showed that s.c. 100 mg anakinra given for a 3-month period led to significant clinical and functional improvement with substantial amelioration of all standard

outcome measures. Over half of the MRI axial enthesitis or osteitis lesions either improved or resolved after anakinra treatment. However, all patients flared 1-2 weeks after withdrawal of therapy (189).

Subsequently, a 24-week open-label trial failed to demonstrate a significant amelioration of clinical, laboratory and imaging outcomes in 20 active refractory patients, with only a small proportion of patients experiencing improvement in spinal symptoms (190).

On the basis of the available data, we formulated the following recommendations:

- Anakinra can not be recommended to treat refractory ankylosing spondylitis (level of evidence IV, strength of recommendation C).

Intra-articular anti-TNF agent treatment

There are 3 RCTs investigating the role of intra-articular anti-TNF- α therapy. None of them showed a significant benefit in terms of clinical response or improvement/resolution of changes on imaging over that provided by intra-articular GC injections (191, 192, 193).

Data from case series and reports may suggest some benefits for intra-articular infliximab but several methodological issues make problematic the assessment of the role of such a treatment.

It has been argued that techniques able to detect the degree of local TNF- α expression, like scintigraphy with radiolabeled-infliximab could be used also to monitor therapeutic response (194). This claim remains to be proven.

a) Intra-articular infliximab

In a large case series, 90% RA patients (10 patients) with refractory monoarthritis had a clinical response both at 2 and 12 weeks after intra-articular (IA) infliximab injection (100 mg for the knee, 50 mg for the ankle, 25 mg for the wrist) (195). Other 4 successful cases of IA infliximab treatment, given twice at a 24-hour interval, were reported in RA active resistant monoarthritis, with evidence of concomitant systemic improvement (196). Seven AS patients treated with intra-articular infliximab for relapsing therapy-resistant

knee monoarthritis were also reported as benefiting from this treatment (194, 197, 198). Systemic improvement was also seen in these patients. Likewise, 9 psoriatic arthritis patients had a good therapeutic response (195, 199), while in a case series on 6 patients treated with intra-articular infliximab an early relapse was noted in the majority of subjects (200). Finally, 6 patients with active refractory unilateral sacro-iliitis have been described, who showed a satisfactory clinical response to a single intra-articular infliximab injection (20 mg) (201, 202).

b) Intra-articular etanercept

In a small pilot study, 26 RA patients were treated with intra-articular etanercept because of monoarthritis flares involving various joints (203). Both clinical and imaging signs improved just after 1 week with sustained benefit, while significant reduction in power Doppler signal and synovial thickness on MRI were reported. On a note of caution, a reaction to intra-articular etanercept interpreted as immune/allergic has been reported (204).

c) Intra-articular adalimumab

There is a case of successful clinical and radiographic response after intra-articular adalimumab administration in a RA patient with persistent refractory knee monoarthritis complicated by avascular necrosis (205).

Two cases with severe knee pigmented villonodular synovitis (PVNS) experienced a marked clinical, functional and ultrasonographic improvement after intra-articular etanercept treatment (206), while another patient with PVNS responded to iv infliximab with complete clinical remission (207).

On the basis of these data, we formulated the following recommendations:

- Intra-articular injections of TNF- α are not recommended to treat refractory arthritis (level of evidence Ib, strength of recommendation A).
- There is insufficient evidence to recommend the use of intra-articular TNF- α inhibitors to treat pigmented villonodular synovitis (level of evidence IV, strength of recommendation C).

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