Does glucocorticosteroid-resistant large-vessel vasculitis (giant cell arteritis and Takayasu arteritis) exist and how can remission be achieved? A critical review of the literature

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ABSTRACT

Introduction. *The mainstay in the treatment of the large-vessel vasculitides giant cell arteritis (GCA) and Takayasu arteritis (TA) are glucocorticosteroids (GC) for induction of remission as well as for its maintenance in low doses for 1 to 2 years. However, clinical practice includes GC-resistant cases without sufficient response to standard GC for induction of remission and GC-dependent cases where a dose reduction of GC without relapse is impossible after successful induction of remission. The aim of this study was to evaluate the data on treatment options in these situations.*

Materials and methods. *A literature search in PubMed matching the terms TA and GCA as well as temporal arteritis with all possible immunosuppressive and biological agents as well as with the terms "treatment, therapy and management" was performed.*

Results. *Sixty-four publications were found. Five case series described large cohorts of patients with GCA (n=2) or TA (n=3) showing that 40.8 % to 48% of GCA patients and 46% to 84% of TA patients require additional immunosuppressive agents to achieve remission and taper GC.*

Most were on biologic agents (mainly infliximab, 24 publications / 123 patients), followed by methotrexate (MTX) (14/113), cyclophosphamide (CYC) (9/27), azathioprine (AZA) (8/51), cyclosporine A (CSA) (6/47), mycophenolate mofetil (MMF) (3/32), leflunomide (LEF) (2/2), chlorambucil (1/1) and antimalarials (1/36). There were also 2 case reports on autologous stem cell transplantation. The distribution of the two entities TA and GCA was as follows: MTX: 98% GCA, 2% TA; IFX: 26.8% GCA, 73.2% TA; CYC: 70.4% GCA, 29.6% TA; AZA: 100% GCA; LEF: 100% TA; MMF: 100% TA; antimalarials: 100% GCA, autologous stem cell transplantation: 100% TA.

A distinction between GC-resistant and GC-dependent cases could not be made from the data available. However, 50 (79%) of the publications described GC-resistant cases. Whereas almost all case reports and retrospective case series (with the exception of CSA) revealed steroid-sparing effects, the 3 prospective randomised trials and 2 open prospective controlled trials on MTX gave conflicting results. However, a recent meta-analysis which recalculated the original data resulted in superiority of MTX after 24 months, there were less relapses and lower GC doses in the MTX group. The prospective controlled IFX trial where IFX was randomised against placebo after GC-induced remission of GCA did not show advantages for IFX over GC alone for maintenance of remission. The prospective controlled ETA trial, which comprised 17 GCA patients, showed small, non-significant advantages but was too small to draw definite conclusions.

Conclusion. *Although GCA is the commonest systemic vasculitis, prospective randomised trials on steroid sparing agents are rare and mostly included only small patient numbers. Inclusion and response criteria were heterogeneous, and observation periods and follow-up were often short. Criteria for GC-resistance or GC-dependence and for disease remission have not been uniformly defined. There is still an urgent need for prospective randomised trials with larger patient groups, longer follow-up and well defined inclusion criteria and criteria for response and*

relapse, using standardised disease activity scoring systems, in order to be able to give evidence-based recommendations for patients not responding to GC alone in the future.

Introduction

Primary large-vessel vasculitides by definition affect the aorta and its branches and include giant cell arteritis (GCA) and Takayasu arteritis (TA). These are distinct disorders with different ages of onset and ethnic distributions as well as HLA associations. However, histopathology is similar: a granulomatous vasculitis with giant cells (1). There are distinct ACR classification criteria for both disorders (2-4). More recently, EULAR recommendations for the management of large-vessel vasculitis have been published (5). Early initiation of high-dose GC therapy (1 mg/kg bodyweight (bw/day) for induction of remission is recommended. The experts also recommend that an immunosuppressive agent should be considered as adjunctive therapy. In the more detailed description, it is stated that methotrexate may be used in GCA, azathioprine (AZA) in TA, and also cyclophosphamide may be effective in glucocorticosteroid (GC) resistant TA. Infliximab (IFX) is said not to be effective as far as relapse rate is concerned and hence is not recommended. The authors recommend the use of low-dose aspirin in all patients with GCA because of an increased risk of cardiovascular and cerebrovascular events.

Obviously, as some of the articles (pp. S70, S130) in this issue of *Clin Exp Rheumatol* show, when treated exclusively with GC, a considerable number of patients do not achieve remission of disease activity – which would be called GC-resistance – or GC cannot be reduced below 7.5 mg prednisolone equivalent in a justifiable amount of time without relapse. The latter would be called GC-dependence. Higher doses of GC (more than 10 mg prednisolone equivalent) over a longer period of time (more than 6 months) are associated with a high risk of adverse effects, which have been well documented in patients with GCA/TA. Up to 86% of GCA patients have been affected by GC-related side effects (6-8). Long-term GC use appears to be associated with an increased risk of severe and opportunistic infections (6), and an increased mortality rate within the first months of initial high dose GC treatment as well as with daily maintenance doses over 10 mg prednisolone equivalent has been described (6, 9-11). Furthermore, there appears to be a subclinical disease activity with an incidence of large artery stenosis and aortic aneurysms or dissections of about 25% during follow-up, and active aortitis was demonstrated in the majority of cases of fatal aortic dissection (12-16).

Hence, steroid-sparing treatment and agents with potent remission-inducing capabilities may be needed.

Methods

We conducted a literature search by PubMed with the key words "giant cell arteritis", "Takayasu arteritis", "large-vessel vasculitis", "temporal arteritis", each connected with each of the following: "treatment", "management", "therapy", "methotrexate", "azathioprine", "cyclosporine A", "leflunomide", "mycophenolate", "mycophenolic acid", "cyclophosphamide", "anti-TNF", "infliximab", "etanercept", "adalimumab", "golimumab", "certolizumab", "tozilizumab", "rituximab", "abatacept".

The articles found were read thoroughly, classified by type (prospective trial, randomised, non-randomised, controlled, uncontrolled, case series, case reports) and disease (GCA or TA), and evaluated for dosages used and responses achieved, as well as for previous treatments the patients had been resistant to.

Results

Sixty-four articles were found (Table I), 14 for MTX (1-98 patients), including 5 randomised trials and 2 prospective open-label studies (17-30), 8 for AZA (1-10 patients), including one prospective placebo-controlled trial and one prospective trial prematurely stopped due to suspected adverse events (AE) and inefficacy (24, 31-39), 6 publications for cyclosporine A (CSA) (1 to 60 patients, including one prospective randomised open trial) (40-45), 2 case reports for leflunomide (LEF) (46, 47), 3 case series for mycophenolate mofetil (MMF) (3 to 21 patients) (48-50), 9 for cyclophosphamide (CYC) (1 to 10 patients) (51-59). One single publication was a retrospective case series on antimalarials (hydroxychloroquine, HCQ) as primary steroid-sparing agent, which did not add efficacy (60), overall recovery rate was 58%. Thirty-five articles with 1 to 44 patients described the efficacy of biologic agents, among these none was found for the newer TNF antagonists golimumab and certolizumab and for abatacept. There were 24 publications for infliximab including 1 to 44 patients, including 2 prospective multicentre trials (61-84). Some of the case series described a switch to etanercept (ETA) or adalimumab (ADA), mostly for convenience reasons and not because of inefficacy (65, 70). 3 publications (85, 86) including one prospective trial focused on ETA (17 patients, prospective, double-blind placebo-controlled single centre study) (87), 2 on ADA (case reports) (88, 89), 5 on tocilizumab (TCZ) (1 to 7 patients) (90-94), 3 on rituximab (RTX) (1 to 3 patients) (95-97). In addition, the keywords "management, treatment and therapy" revealed additional literature on the use of chlorambucil (one case report) (98), antimalarials (60), and autologous stem cell transplantation (two cases, one single case of treatment resistant TA described in a case series on vasculitis and in a registry-based analysis) (99-101).

Most of the case series and case reports, especially when biological agents were used, were conducted in patients with TA, whereas the prospective trials almost exclusively included patients with GCA.

Most of the case reports and case series described positive outcomes of the respective rescue/steroid sparing treatment. There were a few exceptions providing negative results or describing the development of newly onset GCA or TA under immunosuppressive treatment for comorbidities such as Crohn's disease (77). In detail, two publications report inefficacy of CYC in 2 patients with TA (51, 56), in the second case report by Simon *et al.*, the patient later died

Table I. Literature overview.

Medication	Type of large-vessel vasculitis	Type of study	Number of patients	Previous treatments	Dosage	Observation period	Response	Year	Authors
A) Non-biologic									
Methotrexate	PMR/GCA	Case series	3, 2 with GCA	PRED resistant, dose reduction impossible	7,5-12,5 mg/week orally	Not given	Remission, GC reduced, sterioid sparing	1989	Krall PL. Mazanec DJ, Wilke WS: methotrexate for corticosteroid-resistant PMR and GCA, *Cleveland Clin J Med* 1989;56: 253-7 (17)
	GCA	Prospective open	11	None, newly diagnosed	10 mg/week orally	22-37 months	10 patients discontinued. GC MTX safe and steroid sparing	1994	Hernandez-Garcia C *et al.*, Scand J Rheumatol 1994, 23:295-8 (18)
	GCA (AT)	Case reports	3 ,1 MTX, 1	Prednisolone Dapsone, 1 AZA	7.5 mg/week orally	Not given	Patient died due to septicemia	1994	Nesher and Sonnenblick Clin Rheumatol 1994; 13:289-92 (19)
	GCA (and PMR)	Prospective open	3 PMR with GCA, 40 PMR alone	Prednisolone, inadequately controlled	7.5 mg/week orally	9 months	No steroid sparing effect in PMR alone. In GCA. May be promising in GCA/PMR	1996	Feinberg HL *et al.*, J Rheumatol 1996; 23:1550-52(20)
	GCA (and PMR)	Randomised double-blind PBO controlled	6 PMR with GCA, 34 PMR alone,	Active untreated (MTX as first treatment in combination with PRED 20mg/day)	7.5 mg/week orally	21 weeks	PRED reduced by 50, median duration pred 47.5 weeks. No steroid sparing effect compared to PBO	1996	Van der Veen MJ *et al.*, Ann Rheum Dis 1996; 55:218-223 (21)
	TA	Case report	1 child with TA (4 ys)	2mg/kg PRED, ineffective, comb. MTX	10 mg/m^2 /week orally	12 months	PRED successfully tapered, no AE	1998	Shetty *et al.*, Clin Exp Rheumatol 1998; 16:335-336 (22)
	GCA	Prospective, randomised, PBO controlled trial	22 patients with ocular manifestations	Newly diagnosed with severe ocular manifestations PRED/PBO against PRED/MTX	10 mg/week orally after 4–6 weeks of PRED monotherapy (randomised). PRED dose diverse 30-1000 mg after clinical judgement	12 months	High/Megadose GC can be given to elderly pat. Without increasing complications, may improve final VA. MTX not steroid sparing in this setting	1999	Kupersmith *et al.*, Br J Ophthalmol 1999;83:796-801 (23)
	GCA	Prospective, double-blind, PBO controlled (single centre)	21	Newly diagnosed, active. All 40–1000 mg PRED initially	7.5 mg /week orally., in case of flare during pred reduction increase to up to 20mg/week	12 months	No steroid sparing effect of MTX, no difference in AE	2001	Spiera *et al.*, Clin Exp Rheumatol 2001;19:495-501 (26)
	GCA	Randomised, double-blind, PBO-controlled, two centres	42	Newly-onset active. All treated with PRED 60 mg/day p.o. initially	10mg/week orally	24 months	Reduction of no of relapses in MTX group. Siginificantly less cumulative GC in MTX group. No difference in AE	2001	Jover *et al.*, Ann Intern Med 2001; 134:106-114 (27)
	GCA	Multicentre randomised, double-blind, PBO-controlled	98	Active untreated. Add. PRED 1mg/kg/day in both groups	15mg/week p.o.	12 months	No reduction of risk of treatment failure by MTX, no differences for remissions, morbidity, cumulative PRED dose, toxicity. Less PMR relapses in MTX group	2002	Hoffman *et al.*, Arthr Rheum 2002; 46:1309-1318 (25)
	TA	Case report	1 child 6 ys TA	PRED only partially effective	10 mg/m^2/week p.o.	Not given	Steroid sparing and remission inducing effect	2001	Besson-Léaud *et al.*, Archives de Pediatrie 2001; 8:724-7272 (24)
	GCA (AT)	Case report	1	Ocular/cranial arteritis, severe, PRED dependent	10 mg/week	12 months	Remission	2006	Zachariades *et al.*, Oral Surg Oral Med Oral Pathol oral Radiol Endodod 2006; 102:192-197 (30)
	GCA	Case reports	2 patients under MTX for RA	GCA occurred under MTX for RA	12.5 mg/week orally	Not given	Occurrence of GCA under MTX for RA	2006	Rimar *et al.* J Rheumatol 2006; 33:1458-1459 (29)
	GCA	Case series	5 PMR/GCA overlap	GC resistant (Def.: no reduction below 7.5 mg PRED possible)	10–15 mg/week orally	10,7 months (median)	Effect controlled by FDG-PET. Inflammation controlled in all by add. of MTX	2010	Camellino *et al.* *Clin Exp Rheumatol* 2010; 28: 288-289 (28)
Azathioprine	GCA (AT)	Case report among others with neurological manifestations	1	Primary treatment in combination with GC	200 mg/day, PRED 1 mg/kg	Not given	Effective	1969	Moeschlin S. Schweiz Med Wschr 1969; 99:1632 (31)
	GCA (AT)	Case series	2	Tongue necrosis, ocular manifestation and scalp necrosis	100 mg/day, PRED 1 mg/kg	Not given	Effective, remission	1972	Reuther *et al.*, Nervenarzt 1972;43:257 (32)
	GCA (AT)	Case series	15, 6 treated with AZA	Reason for AZA: "complications" under PRED	100 mg/day orally	Not given	PRED reduction possible after addition of AZA	1972	Wagner *et al.*, Med. Welt 1972; 23:641 (39)

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	GCA (AT)	Case series	2	80 mg fluorocortolone, ineffective in 1, AE in 1	150 mg/day	6–12 months	AZA steroid-sparing	1975	Wenig und Meiser, Nervenarzt 1975; 46:453-457 (33)
	GCA (AT)	Case series, retrospective	10, 5 with biopsy-proven AT in addition to PMR	Newly diagnosed, all received PRED 40mg/day	150mg/day orally	6 months	Relapses in 9 after discontinuation of PRED. AZA not steroid sparing	1977	Loevschall et al, Ugeskr Laeg. 1977;139:2618-2620 (34)
	GCA	Prospective, double-blind, PBO-controlled, single centre	31, not differentiated between GCA/PMR or overlap	Under 5 mg PRED or more, controlling symptoms, stable for at least 3 months	1.5–2.7 mg/kg orally./day	52 weeks	PRED reduction more prominent in AZA group, significant at week 52	1986	De Silva et al., Ann Rheum Dis 1986; 45:136-138 (35)
	GCA (AT)	Prospective, randomised PRED alone vs. AZA plus PRED, single centre. Prematurely stopped due to AE and inefficacy of AZA	12	2/7 jaundice under AZA, ineffective in 3/5of the following patients – patient number not precisely provided, brief letter	100–150 mg/day	Planned: 12–18 months	Stopped prematurely due to AE and inefficacy of AZA	1995	Gonzalez-Gay et al., 1995; Rev Rheum Ed Francaise 62:568 (36)
	GCA	Case report	Gential tract, AT	Primarily PRED plus AZA	100 mg	5 months	Remission, PRED tapered	1996	Inanc et al., J Rheumatol 1996; 23:393-395 (37)
	GCA (TA)	Case report	1, ulcerative keratitis	PRED resistance (60 mg)	100 mg, in parallel Pred augmented to 3x1 g iv.	3 months	Improvement, GC weaned	2009	Papathanassiou et al., Eur J Ophthalmol 2009; 19:866-869 (38)
Antimalarials	GCA	Retrospective case series	36	18 primary add. GC, 15 secondary after unability to reduce GC (dependence)	HCQ 400 mg/day	5 ys (mean)	Recovery rate 58%	1994	Le Guennec et al., Rev Rheum ED Fr 1994, 61.485-490 (60)
Cyclosporine A	GCA, TA	Case reports	2 (1 GCA, 1 TA)	Resistant to PRED 100 mg/day	100 ng/ml serum level	Not given	PRED reduction possible, remission	1985	Wendling et al., Arthr Rheum 1985; 28:1078-1079 (40)
	TA	Case report	1	Resistant to PRED 100 mg/day	130 ng/ml serum level	Not given	PRED reduction possible, remission	1992	Pèrez Garcia et al., Revista Clinica Espanola 1992; 190:470-471 (41)
	GCA	Randomised, controlled single centre	22	GCA with impossibility of tapering PRED	2mg/kg bw	6 months	No difference between groups	1998	Schaufelberger et al., Br J Rheumatol 1998; 37:464-465 (42)
	TA	Case report	1 child 13 ys	Active disease in spite of 0,5 mg/kg PRED	70–100 ng/ml serum level	4 ys	Remission, reduction of PRED possible, no AE	1999	Horigome et al.,MJA 1999;170: 566 (43)
	GCA	Prospective randomised open multicentre trial. Control: PRED alone	60	Newly diagnosed, previously untreated	2.18mg/kg (mean)	12 months	No difference between the 2 groups, higher rate of AE in CSA group	2006	Schaufelberger et al, Scand J Rheumatol 2006; 35: 327-329 (44)
	GCA (AT)	Case report	1	Newly diagnosed, severe (tongue necrosis)	100mg	3 months	Remission	2007	Schulz Maahs et al., Braz J Otorhinolaryngol 2007;73:717 (45)
Leflunomide	TA	Case report	1	Resistant to PRED and MTX	20 mg/day	6 months	Remission, PRED tapered, slow response	2001	Haberhauer et al., Clin Exp Rheumatol 2001; 19:477-478 (46)
	TA	Case report	1	PRED resistant, resistant to CYC, CSA, MMF, MTX, IFX. Remission under adalimumab and LEF	20 mg/day	Not given	Remission and delivery of a healthy baby in spite of LEF	2008	Kraemer et al., Hypertension in Pregnancy 2008, 27:247-252 (47)
Mycophenolic acid/ Mycophenolate Mofetil	TA	Case series, retrospective	3	Dependent on high doses of PRED, 2 pre-treated with CYC, CSA, MTX	MMF 2000mg/day	11–15 months	Remission and reduction of PRED in all	1999	Daina et al., Ann Intern Med 1999; 130:422-426(48)
	TA	Case series, retrospective	13, 10 evaluated	Persistent disease activity despite PRED and /or other immunosuppressive drug or reactivation under PRED reduction or unacceptable PRED AE. 50% pre-treated with other immunosuppressives	MMF 2000 mg/day	23.3 months (mean)	Significant decrease in PRED dose and reduction of disease activity in all	2007	Shinjo et al., Clin Rheumatol 2007;26:1871-1875 (49)
	TA	Case series, retrospective	21	55% MMF as initial treatment, rest had AZA before.	MMF dosage not given	9.6 months (mean)	Significant decrease in disease activity as measured by ITAS (Indian Takayasu Arteritis activity score), only 2 MMF AE. Significant decrease in steroid dosage	2010	Goel et al., Clin Rheumatol 2010; 29:329-332 (50)
Cyclophosphamide	TA	Case report	1	PRED ineffective	1 mg/kg/day orally	4 months	Ineffective	1985	Jimenez-Alonso et al., Drug Intelligence and Clin Pharmacy 1985; 19:477 (51)

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	GCA	Case series, retrospectve	4	Severe complications in spite of high dose PRED (1mg/kg bw/day)	0,5-1mg/kg bw orally./ day	6-15 months	No severe AE, good control, in 2 patients treatment completely discontinued in remission after 2-3ys	1986	Pena Sanchez de Rivera et al., Medicina Clinica 1986; 86:306 (52)
	GCA	Case series retrospective	4	Resistant to 6-MP	CYC pulses i.v., 0,5 to 1 g, total of 3 g in 3 weeks.	10-21 months	Stabilised (2) or remission (2), PRED tapered. Rapid response in responders	1992	De Vita et al., J Intern Med 1992; 232:373-375 (53)
	GCA (AT)	Case series, retrospective	4 (1 with CYC)	With severe cerebral manifestations	CYC 75 mg orally/day	Not given	Stabilisation, PRED reduced	1994	Büttner et al., Eur Neurol 1994; 34:162-167 (54)
	TA	Case report	1	Ocular TA resistant to PRED	Monthly iv CYC pulses 500mg/m^2 x 10	Not given	Improvement of visual acuity	2002	Rodriguez-Hurtado et al., Eur J Med Res 2002; 7:128-130 (55)
	GCA	Case report	1	Ocular AT with normal ESR, steroid dependent, reduction or PRED under 10 mg impossible	150 mg/day orally	2 months	Improvement of VA (loss of vision was reversible)	2003	Calgüneri et al., Yonsei Medical Journal 2003; 44:155-158 (59)
	TA	Case report	1	With mesenteric arteriitis resistant to PRED, reduction impossible	CYC (FAUCI) orally	10 months	CYC ineffective, patient died later under ETA due to Candida sepsis	2005	Simon et al., Z Rheumatol 2006; 65:520-526 (56)
	TA	Case series, prospective, open MTX vs. CYC add. to Pred, followed by MTX for maintenance	6 children	Newly diagnosed TA	MTX 12,5 mg/m^2/week orally., CYC 1,5-1,7 mg/kg orally./day	12-18 months	No SAE, all responded and were in remission	2007	Özen et al., J Pediatrics 2007; 150:72-76 (57)
	GCA/TA	Case series, retrospective	10 (4 TA, 6 GCA)	Resistant to high dose PRED, Dose reduction impossible, pretreatment with AZA or MTX ineffective in 6), 2 newly diagnosed, severe manifestations no pretreatment	CYC(NIH) 750 mg /m^2 i.v. every 3 weeks 6-12x, individually adapted (500-900 mg/m^2). Maintenance in all with PRED / AZA, MTX/AZA (1) or MMF/AZA (1)	16 – 45 months	Remission in all but one, also documented by PET/CT	2011	Henes et al., Clin Exp Rheumatol 2011; 29 (suppl. 64):S43-S48 (58)
Chlorambucil	GCA	Case report	1 with add. renal amyloidosis		Chorambucil dosage not given	Not given	Response of GCA (AT) not given, focused on amyloidosis	2001	Moraga et al., Clin Nephrol 2001; 56:402-406 (98)
B) Biologic									
B.1) Anti-TNF Infliximab	GCA	Case series,	4	Severe disease, PRED resistant retrospective	3 infusions of IFX 3mg/kg bw week 0, 2, 6	5-6 months	3 complete response, 1 partial response, later relapse	2001	Cantini et al., Arthr Rheum 2001; 44:2933-2935 (61)
	GCA	Case series	2	Primary treatment in newly diagnosed GCA with IFX	3mg/kg bw i.v. week 0,2,4, then every 8 weeks. NO PRED	Not given	1 complete and rapid response, 1 relapse under IFX, then start PRED	2003	Andonopoulos et al., Ann Rheum Dis 2003; 62:1116 (62)
	TA	Open-label multicentre prospective trial	15	Majority of patients resistant to MTX, MMF, AZA, CYC, 5 PRED resistant only	7 patients ETA 2 x 25 mg sc./week changed later to IFX, 8 IFX 3-5 mg/kg bw i.v. week 0,2,4, every 8 weeks	21.7 months median	25% sustained remission and PRED discontinued. 27% partial remissions, PRED reduced by at least 50%	2004	Hoffman et al., Arthr Rheum 2004; 50: 2296-2304 (63)
	GCA	Case report	1	Monotherapy with IFX because of diabetes	5 mg/ kg bw, intervals not given	6 months	Complete response	2005	Uthman et al., Clin Rheumatol 2006; 25:109-110 (64)
	TA	Case report	1	Resistant to high dose PRED and CYC pulses, oral CYC.	3 mg/kg bw i.v. week 0, 2, 4, ever 8 weeks. Later switch to ADA due to development of ANA (in remission)	8 months	Complete response	2005	Tato et al., International Angiology 2005; 24:304-307 (65)
	TA	Case series, retrospective	2	Reduction of PRED not possible without relapse, in one case also resistance to MTX	3 mg/kg bw i.v. week 0, 2,4, the every 8 weeks with MTX 15 mg/week	Not given	Good clinical response, normalisation of ESR and CRP, ultrasound and MRA	2005	Della Rossa et al., Rheumatology 2005; 44:1074-1075 (66)
	TA	Case report	1	Uveitis in TA resistant to PRED and MTX	3 mg/kg bw i.v.	12 months	Complete response, PRED tapered, MTX discontinued	2005	Meenakshi et al., Journal of Clin Rheumatol 2005; 11:213-215 (67)
	TA	Case report	1	Refractory to PRED and MTX	3 mg/kg bw i.v.	24 weeks	PRED tapered. Remission achieved	2006	Tanaka et al., Internal Medicine DOI:10.2169/ internalmedicine. 45.1377 (68)
	TA	Case series	4	Refractory to PRED, MTX, AZA, MMF, CYC, primary treatment in one	3 mg/kg bw i.v.	22 weeks to 3 years	PRED tapered, remission in all but one	2007	Karageorgaki et al., Clin Rheumatol 2007; 26:984-987 (69)
	GCA (ION)	Case report	1	Ocular manifestation, PRED resistant	3 mg/kg bw i.v. 2 x, then switch to ETA for convenience (25 mg 2x/week s.c.)	Not given	Complete remission, visual acuity stable	2007	Torrente et al., Intern Med J 2007; 37:280-281 (70)

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	GCA (AION)	Case report	1	Severe ocular manifestation, primary treatment	5mg/kg bw	8 weeks	Improvement	2007	Benucci et al., Recenti Progressi I Medicina 2007; 98:624-626 (84)
	GCA	Multicentre international prospective PBO controlled- IFX for maintenance in GC induced remission	44	Newly diagnosed, no pre-treatment	5 mg/kg bw i.v., week 0,2,6 then every 8 weeks	54 weeks	Sample too small to rule out modest effects. No difference for relapses, remissions, PRED reduction, AE.	2007	Hoffman et al., Ann Intern Med 2007; 146:621-630 (71)
	TA	Retrospective case series	25	PRED reduction impossible	4-10 mg/kg bw i.v., ETA (n=9) 25 mg s.c. every week, 5 both, later switched to IFX	12 months	Remission and discontinuation of PRED in 60%, in 28% tapered below 10 mg. 50% could taper additionally given immunosuppressive agents	2008	Molloy et al., Ann Rheum Dis 2008; 67:1567-1569 (72)
	TA	Retrospective case series	4 children with TA	Resistant to PRED and immuno-suppressives (MTX, AZA CYC) (3), 1 with severe newly diagnosed TA	Two 5 mg/kg bw i.v. plus MTX or AZA, two ADA (40 mg s.c. every 2 weeks)	Not given	Remission and reduction of PRED in all	2008	Filocamo et al., J Pediatr 2008; 153:432-434 (73)
	TA	Case report	1 child	With Crohn`s disease under AZA	5 mg/kg bw	Not given	Remission	2009	El-Matary et al., J Pediatrics 2009; 155:151 (74)
	TA	Case report	1	Unresponsive to conventional treatment (HCQ, ticlopidine), PRED 1 mg/kg bw, MTX 15 mg/week orally	5 mg/kg bw week 0,2,4, then every 8 weeks	2 years	Remission, PRED and MTX reduced	2009	Maffei et al., Eur Rev Med Pharmacol Sci 2009; 13:63-65 (75)
	TA	Combined with Crohn`s	1	Resistant to PRED and AZA	5 mg/kg bw i.v.	Not given	Remission of both diseases, PRED reduced	2010	Calderon et al.,Revista Espanola de enfermedades digestivas 2010; 102:144-148 (76)
	TA	Associated with Crohn`s	1	Development of TA under IFX 5 mg/kg bw		Not given		2010	Katoh et al., Intern Med 2010; 49:179-182 (77)
	TA	Case series, retrospective	15, 3 with IFX. Others remission under AZA, MTX or CYC	PRED reduction impossible despite MTX, AZA CYC	5 mg(kg bw. Iv.v	Not given	Disease control in all	2010	Nunes et al., Bras J Rheumatol 2010; 50:291-298 (78)
	TA	Case series, retrospective	2 children	PRED reduction impossible in spite of additional MTX	5 mg/kg bw i.v.	Not given	Remission, PRED reduction	2011	Buonuomo et al., Rheumatol Int 2011; 31:93-95 (79)
	TA	Case series, retrospective	2	Development of TA under IFX 3 mg/kg bw i.v. and MTX, one case later effectively treated with ADA	3 mg/kg bw	Not given		2011	Osman et al., Clin Rheumatol 2011; 30:703-706 (80)
	TA	Case report	1	Patient with ulcerative colitis under bolus steroids and sulfasalazine	5 mg/kg bw week 0,2,4, then every 8 weeks	Not given	Remission	2011	Gecse et al., Inflamm Bowel Dis 2011; 17:E69-70 (81)
	TA	French multicentre study, retrospective case series	15	Active disease in spite of GC and additional immunosuppressive agents (7 MTX, 4 AZA)	3-5 mg/kg bw /week 0,2,4, then every 8 weeks	12 months	Partial or good response in 87% at 3 months and 73% at 12 months. Clinical and biological activity decreased significantly, as did GC dose. AE: one tuberculosis, one severe infection, 2 infusion reactions	2011	Mekinian et al., Rheumatology in press (82)
	TA	Case series, retrospective	5 plus literature review of 79	Resistant to PRED, AZA, MTX	5 mg/kg bw i.v.	3-32 months	Remission, PRED tapered in 3, one AE (cardiac failure)	2011	Comarmond et al., Autoimmunity Reviews 2011; IN PRESS (83)
Etanercept	GCA (AT)	Case report	1	Resistant to high dose GC	25 mg 2x/week s.c.	Not given	Patient stopped ETA thinking to be cured with consecutive relapse, after 6 months remission with 5 mg PRED	2003	Tan et al., Ann Rheum Dis 2003; 62:373-374 (85)
	GCA	Case report	1	Occurrence of GCA under MTX and ETA for RA	25 mg 2x/week s.c.	Not given	Further course not given	2004	Seton J Rheumatol 2004; 31:1467 (86)
	GCA	Prospective, doeuble-blind PBO controlled study single centre	17	GC side effects	25 mg 2x /week s.c.	12 months	50% in ETA group without PRED, 22,2% in PBO group (significant) and in remission	2008	Martinez-Taboada et al., Ann Rheum Dis 208; 67:625-630 (87)
Adalimumab	GCA (AT)	Case report	1	Resistant to 60 mg PRED (ocular manifestation)	Not given, probably RA standard (40 mg c.c. every 2 weeks)	6 months	Complete remission, PRED reduced to 12.5 mg/day	2007	Ahmed et al., Clin Rheumatol 2007; 26:1353-1355 (88)
	GCA	Case report	1	Patient with AT resistant to PRED MTX and ETA switched to ADA for RA	Not given	Not given	Development of GCA under ADA /PRED	2007	Leydet-Quilici et al., Joint Bone Spine 2007; 74:299-305 (89)

Medication	Type of large-vessel vasculitis	Type of study	Number of patients	Previous treatments	Dosage	Observation period	Response	Year	Authors
B.2.) Anti-IL-6									
Tocilizumab	TA	Case report	1	Resistant to high dose PRED and i.v. MP	4 mg /kg bw every 4 weeks i.v., later increased to 8 mg	Not given	Remission, PRED reduced	2008	Nishimoto et al., Arthr Rheum 2008; 58:1197-1200 (90)
	GCA/TA	Case series, retrospective	7 (2 TA, 5 GCA)	Resistant to PRED and MTX (2), PRED alone (2), PRED, AZA MTX, IFX (1), Primary treatment in 2	8 mg/kg bw every 4 weeks	3 months (MRA)	Remission, PRED reduced in all	2011	Seitz et al., Swiss Medical Weekly 2011; 141; w13156 (91)
	GCA	Case series, retrospective	3	Rescue treatment after PRED resistance and contraindications to MTX, AZA and other immuno-suppressive agents	8 mg/kg bw every 4 weeks i.v.	Not given	Remission also proven by PET/CT	2011	Beyer et al., Ann Rheum Dis 2011; 70:1874-1875 (92)
	GCA	Case series	2	PRED and MTX resistant/ dependant (PRED could not be reduced below 25 mg without relapse)	8 mg/g bw every 4 weeks i.v.	7 months	Remisison, tapering of PRED	2011	Sciascia et al., J Rheumatol 2011 38:2080-2081 (93)
	GCA / TA	Case series, retrospective	4 (2 TA, 2 GCA)	Resistant to high dose PRED and MTX	8 mg/kg bw every 4 weeks	7-11 months	Remission, PRED reduced, Remission also proven b PET/CT	2012	Salvarani et al., Reumatology 2012; 51:151-156 (94)
B.3.) Anti-B-Cell									
Rituximab	GCA	Case report	1	Resistant to PRED, AZA not tolerated	1000 mg once i.v.	1 month	Remission also proven by PET, one month later severe bilateral pneumonia with consecutive persistent respiratory problems	2005	Bhatia et al., Ann Rheum Dis 2005; 64:1099-1100 (95)
	GCA	Case report	1	GC could not be tapered due to additional neutropenia	1000 mg day 1 and 15 i.v.	1 month (too short as the authors state themselves)	Therapeutic response not reported, no AE.	2007	Mayrbaeurl et al., Clin Rheumatol 2007; 26:1597-1598 (96)
	TA	Case report	3	Article on B cell homeostasis in TA, 3 of 17 patients treated with RTX. These were resistant to	1000 mg day 1 and 15 i.v.	Online supplement Ansehen	All in remission, also proven by PET/CT	2012	Hoyer et al., Ann Rheum Dis 2012; 71:75-79 and online supplement (97)
C) Other									
Autologous stem cell transplantation	TA	Case report	1	Resistant to PRED, MMF, then stem cell mobilisation and ASCT.	CYC/G-CSF, CYC/ATG	400 days	Remission, off immunosuppression, MRA without activity	2004	Voltarellii et al., Rheumatology 2004; 43:1308-1309 (99)
	TA	Case report in a case series on vasculitides, single centre	1	Resistant to PRED, AZA, YC, MMF, ETA, CSA, IFX, ANAKINRA (various combinations)	CYC/ATG	12 months	Remission, PRED tapered, AZA as maintenance	2005	Kötter et al., Clin Nephrol 2005; 64:485-489 (100)
	TA	Registry data	1 (of 15 wiith vasculitis)	Same patient as above	Same patient as above	16 months		2007	Daikeler et al., Ann Rheum Dis 2007; 66:202-207 (101)
D) MIXED									
	TA	Retrospective single centre series	108	77 patients received GC, 33 in combination with immunosup-pressive drugs such as MTX or AZA.	Not specified	Not given	Survival rate correlates with rate of complications	2005	Park et al., Scand. J. Rheumatol 2005;34:284-292 (104)
	TA	Retrospective case series in multiple centres in Turkey	248	Only 9% treated with GC alone, 84% needed additional immunosuppressives	63% MTX, 22% AZA, 13% CYC, 6% LEF, 4% MMF, 1,2% anti TNF	Not given	Not specified	2009	Bicakcigil et al., Clin Exp Rheumatol 2009; 27 (Suppl. 52) S59-S6 (103)
	TA	Retrospective case series (France) single centre	82	46% required 1 ore more additional immunosuppressive agents (28% AZA, 25.6% MTX, 7,3% MMF, 5,4% monthly CYC pulses. Anti TNF in a single patient (IFX)	Not focused on steroid-sparing treatment	Not given	Not specified, overall survival worse for North Africans	2010	Arnaud et al., Medicine 2010; 89:1-17 (102)

ADA: adalimumab; AE: adverse event; AT: temporal arteritis; AZA: azathioprine; bw: bodyweight; CSA: cyclosporine A; CYC: cyclophosphamide; ETA: etanercept; GC: glcuocorticsteroids; GCA: giant cell arteritis; IFX: LEF: leflunomide; MTX: methotrexate; MMF: mycophenolate mofetil; MRA: magnetic resonance angiography; PRED: prednisolone; MP: methylprednisolone; RTX: rituximab; SAE: serious adverse event; TA: Takayasu arteritis; TCZ: tocilizumab.

of candida sepsis after being switched to ETA. Katoh *et al*. describe a patient with Crohn's disease who developed TA under IFX 5 mg/kg bw, similarly, in a case series by Osman *et al*. 2 patients with Crohn's disease are described, who developed TA under IFX. One of these later was effectively treated with ADA (80). Leydet-Quilici *et al*. describe a patient with rheumatoid arthritis who developed GCA under ADA and prednisolone (PRED) (89). Seton describes a patient developing TA under MTX and ETA for rheumatoid arthritis (86). Rimar *et al*. describe two patients who under treatment for RA with MTX developed GCA (29).

One recent retrospective case series from France described 82 TA patients, 53% (white Caucasian) and 44% (black African) of whom after primary GC treatment required additional immunosuppressive agents. Twenty-eight per cent received AZA, 25.6% MTX, 7.3% MMF, 5.4% monthly CYC pulses. Infliximab was administered to one single patient. As treatment was not in the focus of that study (which examined racial differences in disease activity and outcome), differences in the efficacy of the immunosuppressives are not reported (102). Similarly, in a previous retrospective multicentre analysis of patients with TA in Turkey with 248 individuals, 84% required additional immunosuppressive agents to their primary GC regimen. Most frequently MTX was used (84%), followed by AZA (22%), and CYC (13%). LEF was used in 6% and MMF in 3%. Three resistant cases were treated with TNF inhibitors (103). Another retrospective series with 108 patients from Korea also reported high rate of GC dependent or even resistant cases in TA, with a 48% rate of patients receiving steroid sparing immunosuppressives such as MTX or AZA, which are not specified further (104). In a retrospective single centre analysis from Brazil, of 30 patients only 10 achieved disease control with GC alone. 12 patients received MTX (median 8.8 mg/week) additionally and 58% had a good response, 2 patients resistant to this combination received CYC 2 mg/kg bw/day orally without response (105).

There were prospective open or randomised trials, 6 with MTX, 1 with azathioprine, 3 with IFX and 1 with ETA.

Prospective open and randomised trials

Methotrexate (MTX)

Our literature search revealed two prospective open (18, 20), two single centre prospective controlled double blind trials (21, 26) and two prospective randomised trials with two centres or designed as multicentre trials (25, 27).

The two prospective open trials included 11 and 43 patients, respectively, however, among the 43 patients in the study by Feinberg *et al*., only 3 had GCA, the others were suffering from PMR. Whereas the study by Hernandez-Garcia included newly diagnosed and previously untreated patients, Feinberg *et al*. included patients who were inadequately controlled with prednisolone. The patients in the Hernandez-Garcia study received 10 mg MTX/week orally, those in the Feinberg study 7,5 mg. Garcia-Hernandez *et al*. concluded that MTX is safe and steroid-sparing, as 10 of the 11 patients finally were able to discontinue their GC. The observation period was 22–37 months. In the Feinberg *et el*. trial, with a shorter observation period of 9 months and a lower MTX dosage as well as a difficult-to-treat GC resistant patient population, no steroid-sparing effect for the whole group could be shown. However, as the patient number with GCA was very small, a positive effect of MTX in this subgroup could not be excluded. In the two prospective randomised single centre trials, 40 and 21 patients were included. Also in one of these trials, namely the one published by Van der Veen *et al*., only 6 of the 40 patients had GCA in overlap with PMR, the other 34 patients had PMR only (21). They included patients with active, newly diagnosed and previously untreated disease, the patients in the MTX arm were treated with 7,5 mg MTX/week orally. The observation period was 21 weeks. Spiera *et al*. included 21 GCA patients with active, newly diagnosed and previously untreated disease, the patients in the MTX arm also received 7,5 mg MTX/week orally, but in case of flare this was increased up to a maximum of 20 mg, if necessary. The observation period was 12 months (26). Both studies came to the conclusion that although prednisolone could be reduced by more than 50% of the baseline dosage, MTX has no steroid-sparing effect, as there were no differences between the two arms. Adverse events were not different, either.

Finally, the two prospective two-centre (27) or multicentre (25) trials included 42 and 98 patients respectively. Both included GCA patients who were newly diagnosed, active and untreated. The dosage of MTX in the active treatment arm was 10 and 15 mg/week orally. Both treatment arms received prednisolone, either 60 mg or 1 mg/kg bw. The observation period was 12 months in the study by Jover *et al*. and 24 months in the Hoffman *et el*. trial. The study by Jover *et al*. showed that the number of relapses was significantly reduced in the MTX arm and that the cumulative GC doses were also significantly lower in the MTX treated group. There was no difference in the number of adverse events between the two groups. In contrast, the study by Hoffman *et al*. came to the conclusion that except for a reduction of relapses in the form of polymyalgia rheumatica, MTX did not reduce the cumulative GC dosage, nor did it reduce the number of relapses, the probability of achieving remission or morbidity. Again, there was no difference in adverse events between the groups.

Meta-analysis of the randomised MTX trials

In 2007, Mahr *et al*. published a meta-analysis of the MTX trials published so far (106). They aimed at a re-evaluation of the efficacy and safety of low-dose MTX in GCA. For this purpose, they performed an individual patient data meta-analysis of three of the above mentioned randomised placebo-controlled trials (25-27) with 84 patients in the MTX arms and 77 in the placebo arms of the studies over a median observation period of 54.7 weeks. The trial by van der Veen *et al*. was excluded as the original data were no longer available (21). Use of MTX resulted in a significant reduction in the cumulative GC dose by 842

mg within 48 weeks. Moreover, MTX treatment was associated with a significantly higher probability of achieving sustained discontinuation of GC for more than 24 weeks. Three point six individuals and 4.7 individuals needed to be treated with MTX in order to prevent the occurrence of one first or one second relapse, respectively. MTX reduces the risk of a first relapse by 35% and the risk of a second relapse by 51%. A subgroup analysis according to age, gender, positivity of temporal artery biopsy, relapse type (cranial or non-cranial) and weeks from MTX initiation for relapse did not reveal any differences. The analysis of duration of follow-up at different time points revealed that the superiority of the treatment effect of MTX over placebo appears only after 24 to 36 weeks. The authors conclude that MTX is effective as glucocorticoid-sparing agent and lowers the risk of relapse. It should be considered as a therapeutic option in addition to standard-of-care treatment with GC for patients with GCA.

Azathioprine (AZA)

For azathioprine, only one prospective, double-blind PBO controlled single centre trial was published. It included 31 patients with GCA or PMR/GCA overlap, whose disease activity was controlled with 5 mg prednisolone for at least 3 months. The aim of the study was to show if AZA had a steroid-sparing effect in PMR/GCA overlap during the maintenance phase (35). Sixteen patients were in the AZA arm and 17 in the placebo arm. The patients on AZA received 150 mg daily orally, in combination with prednisolone according to a "standard regimen" which was not specified. However, the patients were stratified according to their prednisolone doses. The observation period was 52 weeks. There was a significant reduction in the prednisolone dose at week 52, in favour of the AZA group.

Cyclosporine A (CSA)

There is one randomised controlled trial with CSA, which included 60 patients with newly diagnosed and untreated GCA. For an observation period of 12 months, the patients all received prednisolone according to a predefined scheme which was not specified in the paper. CSA dosage was 2 mg/kg initially, the dose could be reduced or increased to a maximum of 3.5 mg/kg/day. CSA was reduced by 0.5 mg/day in case of increase in creatinine by more than 30%. There was a high rate of premature termination in the CSA group (11 *vs*. 1) and a high rate of dose reductions of CSA due to adverse events. There was a significant reduction in the GC dose in both treatment groups, there was no difference concerning improvement of clinical and laboratory parameters. The authors conclude that CSA has no steroid-sparing potency in GCA and, additionally, is associated with a high rate of adverse events.

Table II. Distribution of patients on the medications.

Treatment	Total number of patients	GCA	%	GCA resistant	%	TA	%	TA resistant	%
MTX	113	111	98	6	5	2	2	2	100
AZA	51	51	100	3	5.9	0	0	0	0
HCQ	36	36	100	36	100	0	0	0	0
CSA	47	44	93.6	14	52	3	6.4	3	100
LEF	2	0	0	0	0	2	100	2	100
MMF	32	0	0	0	0	32	100	21	65.6
CYC	27	19	70.4	19	100	8	29.6	2	25
IFX	123	33	26.8	5	15.2	90	73.2	82	91
ETA	10	10	100	1	10	0	0	0	0
TCZ	17	12	70.6	10	98.3	5	29.4	5	100
RTX	5	2	40	2	100	3	60	3	100
ASCT	2	0	0	0	0	2	100	2	100

Biologicals

Infliximab (IFX)

Infliximab was the first biologic agent and the first TNF-alpha-antagonist, a chimeric ant-TNF-alpha monoclonal antibody, which was introduced for the treatment of a systemic rheumatic disorder, rheumatoid arthritis, in 1998. The first patients with GCA/TA treated with infliximab were published in 2001. These were 4 treatment resistant GCA patients with very severe, organ- or life-threatening manifestations. Three of the patients achieved remission, 1 was a partial responder who later relapsed (IFX was stopped after 3 infusions) (61). Later, one open-label multicentre prospective trial with 15 patients with TA was published, the majority of the patients included were resistant not only to GC, but also to MTX, MMF, AZA, or CYC. Five of the patients were resistant to prednisolone only. The follow-up was 21.7 months (median). In this study, 7 patients were primarily treated with ETA 2 x 25 mg/week s.c. and 3 switched later to IFX mainly due to restrictions in availability of the drug. The IFX doses varied between 3 mg/kg bw and 5 mg/kg bw week 0, 2, 4, and then every 8 weeks. All patients were said to have received high dose GC initially, however, the exact dosing schedule is not provided. Sixty-seven per cent of the anti-TNF treated patients achieved sustained remission that lasted 1–3.2 years. Twenty-seven per cent achieved a partial remission and were able to reduce their GC requirements by at least 50%. Only one patient did not respond to the TNF antagonist. In 9 of the 14 responders, an increase in the anti-TNF dosage was required to sustain remission. Two relapses occurred during interruption of ETA due to shortage of drug, but remission was re-established upon reinstitution of therapy. Adverse events were comparable in both groups. Anti-TNF is judged by the authors to be a useful adjunct to GC in the treatment of TA.

Three years later, the same group of investigators published a prospective international placebo-controlled multicentre trial in newly onset previously untreated GCA (71). The aim of this study was to analyse if the addition of IFX to standard prednisolone in induction of remission and maintenance would have advantages over PRED monotherapy. The IFX dosage was 5 mg/kg bw, week 0, 2, 4, and then every 8 weeks. Prednisolone

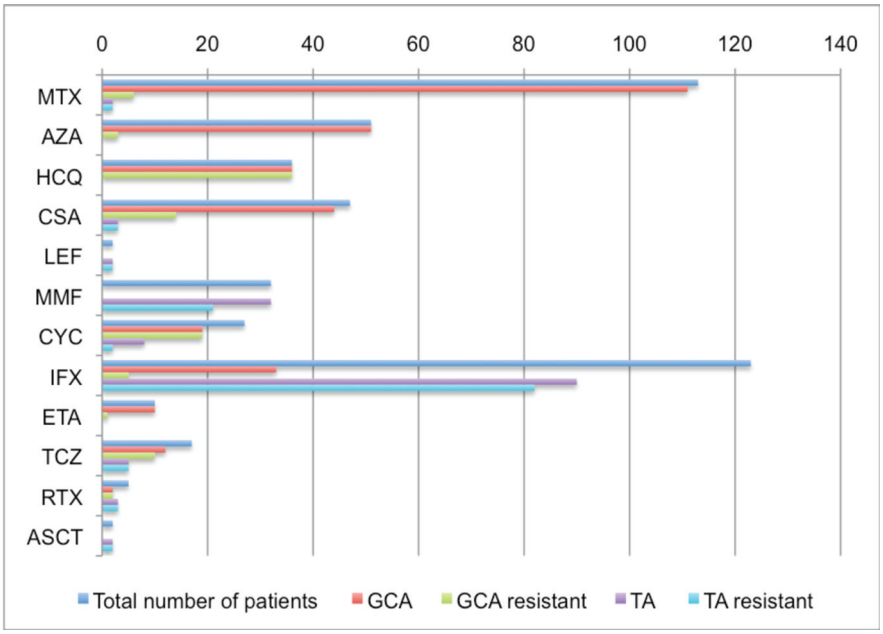

Fig. 1. Distribution of patients on medications. Columns show total number of patients for GCA and TA as well as the number of patients regarded as resistant to GC treatment, respectively.

was started with 40 to 60 mg/day and then reduced according to an algorithm which was provided in the publication. The observation period was 54 weeks, and 22 centres in the USA and Europe participated in the study. The randomisation was 2:1 for IFX. Sixteen patients were assigned to PRED plus placebo, 28 to PRED plus IFX. As a result, IFX did not decrease the number of relapses at week 22, nor did it decrease the cumulative PRED dosage. There were slightly more infections with IFX, but this difference was not significant. In conclusion, the authors state that the sample is too small to rule out modest effects of IFX and included only newly diagnosed patients, however, a role for IFX as a therapeutic agent for maintenance treatment in GCA is unlikely.

Etanercept (ETA)

ETA is a fusion protein of two p75 subunits of the TNF receptor linked to the Fc portion of human IgG1. It was approved for rheumatoid arthritis in 1999. The first case report on ETA for GCA/TA appeared in 2003, however, in the following publications, ETA was given in case series and open prospective studies before or after IFX or in studies where also IFX was analysed (63, 70, 72). In most of these, it proved effective.

There is one randomised prospective double-blind placebo-controlled single centre trial with 17 GCA patients who needed alternative treatments due to GC side effects. They received 25 mg ETA 2x/week s.c. Observation period was 12 months. Eight patients received ETA, 9 PBO. The initial prednisolone dosage varied. After 12 months, 50% of the patients in the ETA group and 22% in the PBO group were able to control the disease without GC therapy (not significant). Patients in the ETA group had a significantly lower dose of accumulated prednisolone during the first year of treatment. There were no differences in number and type of adverse events. The limited number of patients does not allow to draw definitive conclusions, as the authors state.

Summary of data for steroid-resistant or steroid-dependent GCA/TA

Of the 64 publications on steroid sparing immunosuppressives for GCA/TA found in the literature, 50 (79%) reported on patients who were either resistant to or dependent on GC (17, 20, 24, 28, 33, 38, 40, 41, 44, 46-49, 51-53, 55, 56, 58-63, 65-70, 72, 73, 75, 78-80, 82, 83, 85, 86, 88-97, 99, 100).

Among these, there is one prospective trial. It is an open-label trial for TA refractory to immunosuppressives such as MTX, MMF, AZA, CYC, or PRED (5 of 15 patients), who were treated with either ETA or IFX (63).

Of the MTX treated patients reported in the literature, 111 had GCA (98%). Of these, only 6 (5%) were refractory to GC or immunosuppressive agents. Only 2 TA patients were treated with MTX (1.8%), and both were refractory to GC. Fifty-one GCA patients were treated with AZA (100%), only 3 (5.9%) were treatment-resistant. There are no publications on TA patients with AZA. The trial on antimalarials (HCQ) included 36 GCA patients, all (100%) were refractory to standard GC. There are no reports on TA with antimalarials. Fourty-four of the patients with CSA (93.6%) had GCA, only 14 (32%) were treatment resistant. Three TA patients also received CSA (6.8%), all were GC resistant. Two TA and no GCA patients with LEF were published, both were resistant to PRED and MTX or CYC. Exclusively TA patients received MMF (100%), 21 of 32 were resistant to GC (65.6%), 50% also to other immunosuppressives. Nineteen of the patients with CYC had GCA (70.4%), 8 TA (29.6%). All GCA patients (100%) and 2 of the 8 TA patients were treatment resistant (25%), 2 TA and 4 GCA patients were even resistant to MTX or AZA before. As for IFX, 33 patients had GCA (26.8%) and 90 TA (73.2%). Of the GCA patients, only 5 were treatment-resistant (15.2%), mostly to PRED only. Of the TA patients, 82 were treatment resistant (91%), almost all to PRED plus other immunosuppressive agents. For ETA, only GCA patients are reported (n=10, 100%), only one was resistant to higher doses of GC (10%). With TCZ, 12 GCA (70,6%) and 5 TA patients (29.4%) were reported, all but 2 GCA patients (1.7%) had not responded to PRED or PRED plus immunosuppressive agents before. Two GC (40%) and 3 TA (60%) patients have been treated with RTX so far, the GCA patients were all refractory to GC (100%), whereas the TA patients all had received other immunosuppressive agents additionally before. The same also holds true for the 2 TA patients who underwent autologous stem cell transplantation. The percentages of the patients with TA and GCA

for each medication and the percentages of those in each group being GC-resistant are depicted in Figure 1.

There are four larger retrospective case series on the subject of steroid dependency or resistance, one with antimalarials for GCA (36 patients) (60), two on MMF for TA (10 and 21 patients) (49, 50), one on CYC for GCA and TA (10 patients, 4 TA, 6 GCA) (58), one on IFX and ETA for TA (25 patients) (72). For the antimalarials, a "recovery rate" of 58% is described, for MMF significant decreases in disease activity (in the second series measured by the Indian Takayasu Arteritis Activity Score ITAS) and PRED dosage, in the CYC series a remission in all but one patients (90%) also documented by PET/CT, and in the IFX/ITA series a 60% remission rate and 28% significantly decreased PRED dosage is described.

It is impossible to distinguish exactly between GC-resistant and GC-dependent cases, as no clear definitions for resistance or dependency were provided at all or they were very heterogeneous or both were taken together in one series or trial and not regarded separately. Furthermore, the definitions of complete and partial remissions also vary considerably, if specified at all.

Discussion

The mainstay in the management of GCA/TA are high dose GC for induction of remission, and low dose steroids (5 mg PRED /day or lower) for maintenance of remission for 1–2 years, as stated in the recent EULAR recommendations (5). However, in some patients, a reduction of GC under 5 mg/day prednisolone equivalent may be impossible (GC dependency) without relapse or even remission not achievable (GC resistance). This percentage of patients is estimated for GCA to be 40.8% to 48% (7, 107). In these patients, additional remission-inducing agents are needed. Furthermore, additional steroid-sparing agents for maintenance of remission may be necessary in this difficult-to-treat patient population, in order to get the GC dose below the "Cushing threshold" and avoid adverse events such as infections, osteoporosis, diabetes, or cataract. Similarly, 46 to 84% of the TA patients in retrospective case series from Korea, Turkey and France were described to require additional immunosuppressive treatment in order to achieve remission and taper GC (102-104).

Although GCA is the most frequent form of systemic vasculitis, with an annual incidence of 27/100.000 in Scandinavia and 7–11/100.000 in Mediterranean countries (108), as opposed to TA, with an annual incidence of 0.7 and a prevalence of 5–7 per million inhabitants in a recent British study (109), there are only few prospective open or randomised trials on steroid sparing agents for the treatment of GCA or TA resistant to conventional high-dose steroids or requiring prolonged GC doses above the Cushing threshold.

Some trials analysed PMR and GCA simultaneously, which may have hampered the results (20, 21).

MTX is an evidence-based and generally recommended steroid sparing and even remission-inducing agent in granulomatosis with polyangiits (Wegener) (GPA) (110, 111). In the MTX trials for GCA/TA, different patient populations were included (newly diagnosed untreated [18, 25-27], GC resistant [20]). Furthermore, the dosages of MTX were quite low. Most trials and case reports/case series used MTX dosages between 7.5 and 12 mg/week orally. In rheumatoid arthritis, or for the remission inducing treatment of localised forms of GPA (Wegener) (112), higher doses are used (15 mg to 30 mg/week). Another matter of concern is the mode of application of MTX, since probably a parenteral application is more effective compared to oral intake (113) due to better bioavailability (114). The patient numbers in all trials are relatively small. The largest study included 98 patients (25). Observation periods and follow-up, ranging from 3 to 37 months with a median of 11 months may often have been too short to detect differences. There is an intensive debate on the significance and necessity of MTX as a steroid sparing agent in GCA. This is expressed in several critical comments and discussions in the literature over the last 15 years (29, 115, 116). In our opinion, the meta-analysis by Mahr *et al*. (106) clearly shows that MTX should be the first-line agent if a steroid-sparing medication is regarded necessary such as in case of contraindications for GC or impossibility of GC reduction. To clarify if MTX should already be given in combination with the high dose GC for induction of remission to facilitate GC reduction and prevent relapses, further, well-designed and large trials will be necessary. In a recent review in this journal, Spies *et al*. have summarised the available literature on MTX for large-vessel vasculitis and polymyalgia rheumatica and came to the conclusion that 10–15 mg of oral MTX have a modest and delayed effect in reducing relapse rate and lowering the cumulative GC dose. MTX may be used as adjunctive therapy in GC resistance or complications. They suggest that further attempts should be made for a better identification of patients with GC-refractory courses and a more precise formulation of guidelines on indication, optimal dosing and duration (116).

Azathioprine also is widely used as steroid sparing agent not only in connective tissue diseases such as SLE (117, 118), but also in some forms of vasculitis, where the evidence for its efficacy is quite good, such as for example Behçet's disease (119, 120). However, in GCA/TA only one older randomised study is available (35). This revealed a superiority of the AZA arm compared to prednisolone alone in patients with GCA or PMR or both with stable remission of disease under 5 mg prednisolone equivalent or more. Until now, however, no larger multicentre trials followed, possibly because of a risk of elevated liver enzymes.One prospective trial was prematurely stopped because of this adverse event (36).

The use of CSA was discouraged by a randomised study in 2006, which did not show any advantage over placebo but an increase in adverse events (increasing creatinine and hypertension) (44). Leflunomide was not used in a considerable number of patients to date, the same also holds true for chlorambucil. The latter may have too many adverse effects such as cytopenias and secondary malignancy for a

more widespread use. Antimalarials were analysed in a retrospective French study (60), however, there was no placebo control and all patients received GC in parallel. Hence, it is impossible to judge if the recovery rate of 58% has to be ascribed to the antimalarials or not. To date, antimalarials are not recommended for the use in other systemic vasculitides which may be the reason why they were not used by others as a steroid-sparing agent in GCA/TA. Furthermore, the publication appeared in French language, which probably hindered its circulation.

For mycophenolate mofetil (MMF), 3 case series exist, all on TA and almost exclusively steroid dependent patients were treated, one case series also included patients with MMF as initial treatment. In the steroid dependent cases, GC could be decreased, in the case series including also patients with primary MMF treatment GC were also reduced, but it is impossible to differentiate between the effects of GC alone and MMF. Disease activity also decreased in all patients (48-50).

Cyclophosphamide, astonishingly, is not well investigated in GCA/TA, although it is the major remission-inducing agent in severe manifestations of other systemic vasculitides such as GPA (Wegener) (121). Especially in CNS manifestations of Behçet's disease, cyclophosphamide is also recommended (122). There are no prospective controlled trials for GCA/TA, and the largest case series published to date comprises 10 patients, 4 with TA and 6 with GCA (58). Here, 8 patients had refractory disease, 2 severe organ threatening manifestations. All but one achieved remission and prednisolone could be reduced, however, all patients obtained a steroid-sparing maintenance treatment (mostly AZA, some MTX, one MMF). In this case series, remission also was documented by PET/CT. Cyclophosphamide as intravenous pulses according to the NIH (123) or the Eurolupus protocol (124, 125) is relatively safe and effective. In younger patients, fertility may be a matter of concern, as well as secondary malignancies, which tend to occur with an increased frequency at cumulative CYC doses above 30 g (126). Infections, especially in combination with GC, may also be a problem and supportive antibiotic treatment is recommended (cotrimoxazole as prophylaxis against pneumocystis jirovecii pneumonia), as are prophylactic vaccinations (pneumococci, haemophilus, influenza). Here, too a randomised trial for CYC against placebo for induction of remission in patients with severe manifestations of GCA or TA (CNS, ocular, gastrointestinal vessels) would be desirable, especially in the light of cost-effectiveness when compared to biologics.

Concerning biological agents, most reports are on anti-TNF agents, among these, mostly on IFX which was the first one available in 1998. There is one prospective randomised trial with IFX *versus* GC alone for maintenance treatment of newly diagnosed GCA in GC induced remission (71). Another prospective open-label multicentre trial on treatment-resistant TA uses ETA and IFX and later switched some of the ETA patients to IFX. Whereas the randomised study did not find any difference between IFX or placebo and was stopped prematurely, the open trial showed a marked reduction in GC dose and remission rate (partial and complete) of appr. 50% (63). The main difference between the trials (besides the focus on two different entities, namely GCA and TA and the open non randomised trial merges ETA and IFX) is that the randomised trial used IFX as maintenance treatment in patients in remission, whereas the TA patients in the second trial were resistant to PRED or, half of them, also to diverse steroid-sparing immunosuppressives. However, the results of the open-label trial are difficult to interprete as IFX and ETA were not used systematically but merged. ETA may be less effective than IFX, as ETA is a fusion protein of the soluble TNF receptor and IFX a monoclonal antibody against TNF alpha. ETA has been shown to be less effective for uveitis and inflammatory bowel disease than monoclonal anti-TNF alpha antibodies (127-129). The second prospective, randomised placebo-controlled trial uses ETA for GCA patients who due to side effects could not be treated with adequate doses of GC. The ETA group had significantly lower GC doses than the PBO group at the end of the study, and relapse rate also was lower (not significant). The authors conclude that their sample size (17 patients) probably was too small to detect further differences (87). In his editorial comment on the study by Hoffman *et al*. of 2007, Luqmani (130) points out that the confidence intervals were very wide and hence the sample size also in the prospective randomised trial with IFX may have been far too small to detect treatment effects. He proposes a trial for GCA with three treatment groups: standard-dose prolonged GC, short dose GC in combination with IFX and a third arm with placebo only after successful induction of remission with GC.

Most recently, Comarmond *et al*. have published a review of the literature on anti-TNF-alpha agents in refractory TA (83). All patients of 79 with TA except one published in case reports and case series thus far had been inadequately controlled by GC and other immunosuppressive agents before receiving anti-TNF-alpha agents. They would thus probably be classified as "steroid-resistant". The most commonly used anti-TNF agent was IFX in a dosage of 5 mg/kg bw, in combination with either MTX or AZA. Thirty-seven per cent of the patients achieved complete remission, while 53.5% partial remission. GC could be tapered in 52% and discontinued in 40%. Adverse events were observed in 20%, mostly infections, followed by hypersensitivity reactions.

One may hypothesise that anti-TNF agents may be useful in the setting of induction of remission in GC-resistant cases of GCA or TA only, a question which has not been addressed in the prospective trials until now. From an immunological point of view, their use in GCA and TA appears reasonable, as TNF alpha was found in abundance in affected temporal arteries (131).

IL-6 antagonists have been used recently in several case reports and case series. This is reasonable from a pathogenetical point of view, as IL-6 appears to be one of the key players in the pathogenesis of GCA and TA. It is present in the wall of the inflamed vessels (132).

Tocilizumab was mostly applied to patients with treatment-resistant GCA or TA, and to date no inefficacy was reported. Rituximab has been exclusively used in a very limited number of treatment-resistant cases of GCA (n=2) or TA (n=3). Until recently, the role of B-cells in TA and GCA was unclear, and their role in the pathogenesis of large-vessel vasculitides appeared to be limited, as macrophages, dendritic cells and $CD4^{+}CD28^{-}$ T-cells dominate the inflammatory infiltrate and produce IFN gamma, IL-1β, IL-6, TNF alpha and metalloproteinases and induce the production of PDGF. In 2011, Hoyer *et al*. showed that the number and frequency of antibody secreting CD19+/CD20-/CD27high plasmablasts is increased in the peripheral blood of patients with clinically active TA, as well as general B-cell hyperactivity and that these patients can be treated successfully with rituximab (97). Although this at first seems illogical as the plasmablasts are CD20 negative and rituximab binds to CD20, plasmablasts differentiate from CD20+ B-cells, so rituximab depletes their B-cell pool.

As "ultima ratio" autologous stem cell transplantation was performed in 2 patients reported in the literature so far. One had received even cyclophosphamide and anti-TNF agents and almost all available immunosuppressives without clinical effect (100), the other had been refractory to Pred, MTX, MMF (99). Both patients achieved remission after ASCT and were able to reduce their baseline immunosuppressive treatments. GCA patients should not undergo ASCT as they are normally older than 60 years and have comorbidities which unacceptably increase transplantation associated morbidity and mortality. As transplantation associated mortality in autoimmune diseases lies between 3 and 7%, this approach in our opinion should be reserved for otherwise healthy patients with TA who do not respond even to biological agents.

In this issue of *Clin Exp Rheumatol*, Italian recommendations for the treatment of large-vessel vasculitides with biological agents are published (see p. S139). These recommendations show how difficult it is to make definite statements, when clear-cut evidence is missing. The EULAR recommendations for GCA and TA were published in 2009 (5), and until 2011 not much more evidence adding to that underlying the EULAR recommendations appeared. The Italian recommendations focus on biological agents and omit recommendations for alternative steroid-sparing or remission-inducing agents. The only additional major difference between the Italian and the EULAR recommendations is that in the Italian Behçet's disease, Cogan syndrome and isolated CNS angiitis have been included under the headline "large-vessel vasculitis". Normally, the term large-vessel vasculitis is reserved for GCA and TA, two vasculitides which almost exclusively affect the aorta and its major branches. CNS angiitis is mostly affecting small arteries, and Behçet's disease affects vessels of all sizes, also veins, but small vessels are much more commonly affected than large ones. Cogan syndrome is a very special entity consisting of interstitial keratitis or panuveitis associated with inner ear deafness.

For GCA biological agents (namely TNF inhibitors) are not recommended as first line treatment or monotherapy because of lack of evidence. They may be used in patients with more than 2 flares or relapses despite adequate treatment with GC and one or more additional immunosuppressive agents (MTX 15–20 mg/week, AZA 2–2.5 mg/day).

Similarly, for TA due to lack of evidence, no monotherapy with biological agents (TNF inhibitors) is encouraged, nor is the use as first line treatment. They may be used in patients with persisting disease activity for more than 6 months or more than 2 flares or relapse despite GC and one or more immunosuppressive agent (MTX 20 mg/week, AZA 2–2.5 mg/day, MMF 2 g/day for 4–6 months).

For both diseases, the efficacy of biological agents is to be assessed after 4 months and in case of lack of improvement it should be discontinued.

Everybody would agree that there is no evidence for monotherapy with biological agents, and that the evidence for their efficacy as a primary steroid-sparing treatment is sparse. However, with the exception of methotrexate, the evidence for the use of immunosuppressive agents as remission-inducing or steroid-sparing agents is lacking, too. Hence, the recommendations for the immunosuppressive agents, which must have been ineffective before initiating treatment with biological agents, are more eminence- than evidence -based, as are the recommendations for the MTX dosages, because the trials and case series used lower doses of MTX than those recommended by the Italian specialists. One may ask why cyclophosphamide was not considered in the recommendations and why it was not considered as a primary "third-line" agent in steroid resistant or dependent GCA or TA after inefficacy of GC and one less aggressive immunosuppressive agent. To date, it is impossible to decide if CYC has more, comparable or even less adverse effects than anti-TNF alpha biologicals. We suppose that with the EUROLUPUS protocol and adequate antibiotic prophylaxis, this will not be the case, and regarding the existing case series and experiences in other systemic vasculitides it may be as effective but much cheaper than the biologicals. However, this remains to be proven by appropriately designed prospective trials.

In summary, steroid-resistant GCA and TA clearly exist, and prospective randomised placebo-controlled trials for their treatment are urgently needed. Unfortunately, the trials which have been published to date have included very heterogeneous patient groups. The numbers of patients are too small to draw definite conclusions in almost all of them, and in the MTX trials, the dosage of the active medication probably was too low. Furthermore, we suggest to include GC-resistant patients into trials with agents for remission-induction, whereas trials testing GC-sparing properties, should include newly diagnosed patients. Of course, in the case of trials for induction of remission, a uniform and clear-cut definition of GC-resistance is mandatory – as was suggested for GC-dependence by Camellino *et al*. (28) or van der Veen *et al*. (21) who defined GC-dependence and GC-resistance as an impossibility of

reducing prednisolone under 7.5 mg/day or under 20 mg/day, respectively, without increase in disease activity. Moreover, a kind of disease activity score would be desirable, such as for example the Indian Takayasu Arteritis Activity Score (ITAS) used by Goel *et al*. (50). Recently, a Takayasu Disease Extent Score was published (133), which may also be useful for future trials. To our knowledge, for GCA, no such validated clinical activity index was developed so far.

We should focus on developing a strong network of clinicians and researchers interested in GCA/TA and design appropriate prospective randomised trials which hopefully answer the most urgent questions in the future. In this respect, we should follow the example of EUVAS (the European vasculitis study group, http://www.vasculitis.org/), designing, completing and publishing studies on the treatment of ANCA associated vasculitides – this is probably the way to optimise the treatment of patients with large-vessel vasculitides, too.

References

1. MAKSIMOWICZ-MCKINNON K, CLARK TM, HOFFMAN GS: Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? *Medicine* 2009; 88: 221-6.
2. HUNDER GG, BLOCH DA, MICHEL BA *et al*.: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990; 33: 1122-8.
3. HUNDER GG: Classification/diagnostic criteria for GCA/PMR. *Clin Exp Rheumatol* 2000; 18: S4-5.
4. BLOCH DA, MICHEL BA, HUNDER GG *et al*.: The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. *Arthritis Rheum* 1990; 33: 1068-73.
5. MUKHTYAR C, GUILLEVIN L, CID MC *et al*.: EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2009; 68: 318-23.
6. NESHER G, SONNENBLICK M, FRIEDLANDER Y: Analysis of steroid related complications and mortality in temporal arteritis: a 15-year survey of 43 patients. *J Rheumatol* 1994; 21: 1283-6.
7. PROVENA, GABRIELSE, ORCES C, O'FALLON WM, HUNDER GG: Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum* 2003; 49: 703-8.
8. LÓPEZ VIVES LNJ, ESTRADA P, GÓMEZ VAQUERO C, NOLLA M: Adverse outcomes of glucocorticoid tehrapy among patients with giant cell arteritis. *Arthritis Rheum* 2010; 62: S532.
9. GRAHAM E, HOLLAND A, AVERY A, RUSSELL RW: Prognosis in giant-cell arteritis. *Br Med J* (Clin Res Ed) 1981; 282: 269-71.
10. HACHULLA E, BOIVIN V, PASTUREL-MICHON U *et al*.: Prognostic factors and long-term evolution in a cohort of 133 patients with giant cell arteritis. *Clin Exp Rheumatol* 2001; 19: 171-6
11. UDDHAMMAR A, ERIKSSON AL, NYSTROM L, STENLING R, RANTAPAA-DAHLQVIST S: Increased mortality due to cardiovascular disease in patients with giant cell arteritis in northern Sweden. *J Rheumatol* 2002; 29: 737-42.
12. EVANS JM, O'FALLON WM, HUNDER GG: Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. A population-based study. *Ann Intern Med* 1995; 122: 502-7.
13. NUENNINGHOFF DM, HUNDER GG, CHRISTIANSON TJ, MCCLELLAND RL, MATTESON EL: Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthritis Rheum* 2003; 48: 3522-31.
14. BONGARTZ T, MATTESON EL: Large-vessel involvement in giant cell arteritis. *Curr Opin Rheumatol* 2006; 18: 10-7.
15. GARCIA-MARTINEZ A, HERNANDEZ-RODRIGUEZ J, ARGUIS P *et al*.: Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: a cross-sectional screening of fifty-four prospectively followed patients. *Arthritis Rheum* 2008; 59: 422-30.
16. GARCIA-MARTINEZ AAP, PRIETO S, HERNANDEZ-RODRIGUEZ J *et al*.: Outcome of aortic structural damage after long-term follow-up of patients with giant cell arteritis. Cross-sectional screening of 29 prospectivel followed patients. *Ann Rheum Dis* 2010; 69: 689.
17. KRALL PL, MAZANEC DJ, WILKE WS: Methotrexate for corticosteroid-resistant polymyalgia rheumatica and giant cell arteritis. *Cleveland Clin J Med* 1989; 56: 253-7.
18. HERNANDEZ-GARCIA C, SORIANO C, MORADO C *et al*.: Methotrexate treatment in the management of giant cell arteritis. *Scand J Rheumatol* 1994; 23: 295-8.
19. NESHER G, SONNENBLICK M: Steroid-sparing medications in temporal arteritis--report of three cases and review of 174 reported patients. *Clin Rheumatol* 1994; 13: 289-92.
20. FEINBERG HL, SHERMAN JD, SCHREPFERMAN CG, DIETZEN CJ, FEINBERG GD: The use of methotrexate in polymyalgia rheumatica. *J Rheumatol* 1996; 23: 1550-2.
21. VAN DER VEEN MJ, DINANT HJ, VAN BOOMAFRANKFORT C, VAN ALBADA-KUIPERS GA, BIJLSMA JW: Can methotrexate be used as a steroid sparing agent in the treatment of polymyalgia rheumatica and giant cell arteritis? *Ann Rheum Dis* 1996; 55: 218-23.
22. SHETTY AK, STOPA AR, GEDALIA A: Low-dose methotrexate as a steroid-sparing agent in a child with Takayasu's arteritis. *Clin Exp Rheumatol* 1998; 16: 335-6.
23. KUPERSMITH MJ, LANGER R, MITNICK H *et al*.: Visual performance in giant cell arteritis (temporal arteritis) after 1 year of therapy. *Br J Ophthalmol* 1999; 83: 796-801.
24. BESSON-LEAUD L, GRENIER N, BESSON-LEAUD M, BONIFACE C, GUILLARD JM: [Takayasu's disease: interest in methotrexate treatment]. *Arch Pediatr* 2001; 8: 724-7.
25. HOFFMAN GS, CID MC, HELLMANN DB *et al*.: A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002; 46: 1309-18.
26. SPIERA RF, MITNICK HJ, KUPERSMITH M *et al*.: A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin Exp Rheumatol* 2001; 19: 495-501.
27. JOVER JA, HERNANDEZ-GARCIA C, MORADO IC, VARGAS E, BANARES A, FERNANDEZ-GUTIERREZ B: Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001: 134: 106-14.
28. CAMELLINO D, MORBELLI S, SAMBUCETI G, CIMMINO MA: Methotrexate treatment of polymyalgia rheumatica/giant cell arteritis-associated large vessel vasculitis. *Clin Exp Rheumatol* 2010; 28: 288-9.
29. RIMAR D, ROZENBAUM M, ZISMAN D *et al*.: Giant cell arteritis--the methotrexate debate revisited. *J Rheumatol* 2006; 33: 1458-9.
30. ZACHARIADES N, SKOURA C, SPANOU A, MACHERA H: Temporal arteritis: report of a case. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006: 102: 192-7.
31. MOESCHLIN S: [Clinical demonstration of neurological cases. Temporal arteritis, diffuse vasculitis with polyneuritis, periarteritis nodosa, Behcet's syndrome, "subclavian steal syndrome", Wallenberg's syndrome]. *Schweiz Med Wochenschr* 1969; 99: 1632-40.
32. REUTHER R, BETZ H: [Temporal arteritis with ischemic scalp and tongue necrosis]. *Der Nervenarzt* 1972; 43: 257-62.
33. WENIG C, MEISER RJ: [Azathioprine in the treatment of arteriitis temporalis]. *Der Nervenarzt* 1975; 46: 453-7.
34. LOVSCHALL S: [Azathioprine in the treatment of temporal arteritis and polymyalgia rheumatica]. *Ugeskrift for laeger* 1977; 139: 2618-20.
35. DE SILVA M, HAZLEMAN BL: Azathioprine in giant cell arteritis/polymyalgia rheumatica: a double-blind study. *Ann Rheum Dis* 1986; 45: 136-8.
36. GONZALEZ-GAY MA: The quest for the ideal therapy for giant cell arteritis. *Rev Rhum Engl Ed* 1995; 62: 539.
37. INANC M, GUL A, TUZLALI S *et al*.: Female genital tract giant cell arteritis associated with occult temporal arteritis. *J Rheumatol* 1996; 23: 393-5.
38. PAPATHANASSIOU M, ELEZOGLU A, NIKITA E, THEODOSSIADIS PG, VERGADOS I: A rare case of peripheral ulcerative keratitis in temporal arteritis. *Eur J Ophthalmol* 2009; 19: 866-9.
39. WAGNER A, ANNWEILER J, KRAUS E: [Clinical observations in patients with giant cell arteritis, temporal arteritis]. *Die Medizinische Welt* 1972; 23: 641-5.
40. WENDLING D, HORY B, BLANC D: Cyclo-

sporine: a new adjuvant therapy for giant cell arteritis? *Arthritis Rheum* 1985; 28: 1078-9.
41. PEREZ GARCIA C, SANCHEZ ALVAREZ J, HERREROS GONZALEZ J, MARAVI PETRI E: [The long-term treatment of Takayasu's disease with cyclosporin]. *Rev Clin Esp* 1992; 190: 470-1.
42. SCHAUFELBERGER C, ANDERSSON R, NORDBORG E: No additive effect of cyclosporin A compared with glucocorticoid treatment alone in giant cell arteritis: results of an open, controlled, randomized study. *Br J Rheumatol* 1998; 37: 464-5.
43. HORIGOME H, KAMODA T, MATSUI A: Treatment of glucocorticoid-dependent Takayasu's arteritis with cyclosporin. *Med J Australia* 1999; 170: 566.
44. SCHAUFELBERGER C, MOLLBY H, UDDHAMMAR A, BRATT J, NORDBORG E: No additional steroid-sparing effect of cyclosporine A in giant cell arteritis. *Scand J Rheumatol* 2006; 35: 327-9.
45. MAAHS GS, FABRICIO DD: Tongue necrosis in a patient with cranial arteritis. *Braz J otorhinolaryngol* 2007; 73: 717.
46. HABERHAUER G, KITTL EM, DUNKY A, FEYERTAG J, BAUER K: Beneficial effects of leflunomide in glucocorticoid- and methotrexate-resistant Takayasu's arteritis. *Clin Exp Rheumatol* 2001; 19: 477-8.
47. KRAEMER B, ABELE H, HAHN M *et al*.: A successful pregnancy in a patient with Takayasu's arteritis. *Hypertens Pregnancy* 2008; 27: 247-52.
48. DAINA E, SCHIEPPATI A, REMUZZI G: Mycophenolate mofetil for the treatment of Takayasu arteritis: report of three cases. *Ann Intern Med* 1999; 130: 422-6.
49. SHINJO SK, PEREIRA RM, TIZZIANI VA, RADU AS, LEVY-NETO M: Mycophenolate mofetil reduces disease activity and steroid dosage in Takayasu arteritis. *Clin Rheumatol* 2007; 26: 1871-5.
50. GOEL R, DANDA D, MATHEW J, EDWIN N: Mycophenolate mofetil in Takayasu's arteritis. *Clin Rheumatol* 2010; 29: 329-32.
51. JIMENEZ-ALONSO J, NUNO E, MUNOZ-AVILA J *et al*.: Cyclophosphamide failure in Takayasu's disease. *Drug Intell Clin Pharm* 1985; 19: 477.
52. PENA SANCHEZ DE RIVERA JM, BARBADO HERNANDEZ FJ, REDONDO SANCHEZ C, VAZQUEZ RODRIGUEZ JJ: [Is cyclophosphamide useful in the treatment of giant cell arteritis?]. *Med Clin (Barc)* 1986; 86: 306.
53. DE VITA S, TAVONI A, JERACITANO G, GEMIGNANI G, DOLCHER MP, BOMBARDIERI S: Treatment of giant cell arteritis with cyclophosphamide pulses. *J Intern Med* 1992; 232: 373-5.
54. BUTTNER T, HEYE N, PRZUNTEK H: Temporal arteritis with cerebral complications: report of four cases. *Eur Neurol* 1994; 34: 162-7.
55. RODRIGUEZ-HURTADO FJ, SABIO JM, LUCENA J, JIMENEZ-ALONSO J: Ocular involvement in Takayasu's arteritis: response to cyclophosphamide therapy. *Eur J Med Res* 2002; 7: 128-30.
56. SIMON S, SCHITTKO G, BOSENBERG H, HOLL-ULRICH K, SCHWARZ-EYWILL M: [Fulminant course of a Takayasu's arteritis and rare mesenteric arterial maninfestion]. *Z Rheumatol* 2006; 65: 520, 2-6.
57. OZEN S, DUZOVA A, BAKKALOGLU A *et al*.: Takayasu arteritis in children: preliminary experience with cyclophosphamide induction and corticosteroids followed by methotrexate. *J Pediatr* 2007; 150: 72-6.
58. HENES JC, MUELLER M, PFANNENBERG C, KANZ L, KOETTER I: Cyclophosphamide for large vessel vasculitis: assessment of response by PET/CT. *Clin Exp Rheumatol* 2011; 29: S43-8.
59. CALGUNERI M, COBANKARA V, OZATLI D *et al*.: Is visual loss due to giant cell arteritis reversible? *Yonsei Med J* 2003; 44: 155-8.
60. LE GUENNEC P, DROMER C, SIXOU L, MARC V, COUSTALS P, FOURNIE B: [Treatment of Horton disease. Value of synthetic antimalarials. Apropos of a retrospective study of 36 patients]. *Rev Rhum Ed Fr* 1994; 61: 485-90.
61. CANTINI F, NICCOLI L, SALVARANI C, PADULA A, OLIVIERI I: Treatment of longstanding active giant cell arteritis with infliximab: report of four cases. *Arthritis Rheum* 2001; 44: 2933-5.
62. ANDONOPOULOS AP, MEIMARIS N, DAOUSSIS D, BOUNAS A, GIANNOPOULOS G: Experience with infliximab (anti-TNF alpha monoclonal antibody) as monotherapy for giant cell arteritis. *Ann Rheum Dis* 2003; 62: 1116.
63. HOFFMAN GS, MERKEL PA, BRASINGTON RD, LENSCHOW DJ, LIANG P: Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum* 2004; 50: 2296-304.
64. UTHMAN I, KANJ N, ATWEH S: Infliximab as monotherapy in giant cell arteritis. *Clin Rheumatol* 2006; 25: 109-10.
65. TATO F, RIEGER J, HOFFMANN U: Refractory Takayasu's arteritis successfully treated with the human, monoclonal anti-tumor necrosis factor antibody adalimumab. *Int Angiol* 2005; 24: 304-7.
66. DELLA ROSSA A, TAVONI A, MERLINI G *et al*.: Two Takayasu arteritis patients successfully treated with infliximab: a potential disease-modifying agent? *Rheumatology* (Oxford) 2005; 44: 1074-5.
67. JOLLY M, CURRAN JJ: Infliximab-responsive uveitis and vasculitis in a patient with Takayasu arteritis. *J Clin Rheumatol* 2005; 11: 213-5.
68. TANAKA F, KAWAKAMI A, IWANAGA N *et al*.: Infliximab is effective for Takayasu arteritis refractory to glucocorticoid and methotrexate. *Intern Med* 2006; 45: 313-6.
69. KARAGEORGAKI ZT, MAVRAGANI CP, PAPATHANASIOU MA, SKOPOULI FN: Infliximab in Takayasu arteritis: a safe alternative? *Clin Rheumatol* 2007; 26: 984-7.
70. TORRENTE SV, GUERRI RC, PEREZ-GARCIA C, BENITO P, CARBONELL J: Amaurosis in patients with giant cell arteritis: treatment with anti-tumour necrosis factor-alpha. *Intern Med J* 2007; 37: 280-1.
71. HOFFMAN GS, CID MC, RENDT-ZAGAR KE *et al*.: Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med* 2007; 146: 621-30.
72. MOLLOY ES, LANGFORD CA, CLARK TM, GOTA CE, HOFFMAN GS: Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up. *Ann Rheum Dis* 2008; 67: 1567-9.
73. FILOCAMO G, BUONCOMPAGNI A, VIOLA S *et al*.: Treatment of Takayasu's arteritis with tumor necrosis factor antagonists. *J Pediatr* 2008; 153: 432-4.
74. EL-MATARY W, PERSAD R: Takayasu's aortitis and infliximab. *J Pediatr* 2009; 155: 151.
75. MAFFEI S, DI RENZO M, SANTORO S, PUCCETTI L, PASQUI AL: Refractory Takayasu arteritis successfully treated with infliximab. *Eur Rev Med Pharmacolog Sci* 2009; 13: 63-5.
76. CALDERON R, ESTRADA S, RAMIREZ DE LA PISCINA P *et al*.: Infliximab therapy in a patient with refractory ileocolic Crohn's disease and Takayasu arteritis. *Rev Esp Enferm Dig* 2010; 102: 145-6.
77. KATOH N, KUBOTA M, SHIMOJIMA Y *et al*.: Takayasu's arteritis in a patient with Crohn's disease: an unexpected association during infliximab therapy. *Intern Med* 2010; 49: 179-82.
78. NUNES G, NEVES FS, MELO FM, DE CASTRO GR, ZIMMERMANN AF, PEREIRA IA: Takayasu arteritis: anti-TNF therapy in a Brazilian setting. *Rev Bras Reumatol* 2010; 50: 291-8.
79. BUONUOMO PS, BRACAGLIA C, CAMPANA A *et al*.: Infliximab therapy in pediatric Takayasu's arteritis: report of two cases. *Rheumatology Int* 2011; 31: 93-5.
80. OSMAN M, AARON S, NOGA M, YACYSHYN E: Takayasu's arteritis progression on anti-TNF biologics: a case series. *Clin Rheumatol* 2011; 30: 703-6.
81. GECSE K, RUZSA Z, NAGY F, WITTMANN T, MOLNAR T: Successful infliximab treatment in a patient with Takayasu arteritis associated with ulcerative colitis or migration does not override genetics. *Inflamm Bowel Dis* 2011; 17: E69-70.
82. MEKINIAN A, NEEL A, SIBILIA J *et al*.: Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study. *Rheumatology* (Oxford) 2012.
83. COMARMOND C, PLAISIER E, DAHAN K *et al*.: Anti TNF-alpha in refractory Takayasu's arteritis: Cases series and review of the literature. *Autoimmunity reviews* 2011.
84. BENUCCI M, MANFREDI M, PUCE F, ZUCCARINI S: [Improvement in visual acuity in a patient with ischaemic optic neuropathy (Horton arteritis) undergoing therapy with infliximab: a case report]. *Recenti Prog Med* 2007; 98: 624-6.
85. TAN AL, HOLDSWORTH J, PEASE C, EMERY P, MCGONAGLE D: Successful treatment of resistant giant cell arteritis with etanercept. *Ann Rheum Dis* 2003; 62: 373-4.
86. SETON M: Giant cell arteritis in a patient taking etanercept and methotrexate. *J Rheumatol* 2004; 31: 1467.
87. MARTINEZ-TABOADA VM, RODRIGUEZ-VALVERDE V, CARRENO L *et al*.: A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. *Ann Rheum Dis* 2008; 67: 625-30.
88. AHMED MM, MUBASHIR E, HAYAT S, FOW-

LER M, BERNEY SM: Treatment of refractory temporal arteritis with adalimumab. *Clin Rheumatol* 2007; 26: 1353-5.
89. LEYDET-QUILICI H, LUC M, ARMINGEAT T, PHAM T, LAFFORGUE P: Giant cell arteritis during adalimumab treatment for rheumatoid arthritis. *Joint Bone Spine* 2007; 74: 303-4.
90. NISHIMOTO N, NAKAHARA H, YOSHIO-HOSHINO N, MIMA T: Successful treatment of a patient with Takayasu arteritis using a humanized anti-interleukin-6 receptor antibody. *Arthritis Rheum* 2008; 58: 1197-200.
91. SEITZ M, REICHENBACH S, BONEL HM, ADLER S, WERMELINGER F, VILLIGER PM: Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. *Swiss Med Wkly* 2011; 141: w13156.
92. BEYER C, AXMANN R, SAHINBEGOVIC E *et al*.: Anti-interleukin 6 receptor therapy as rescue treatment for giant cell arteritis. *Ann Rheum Dis* 2011; 70: 1874-5.
93. SCIASCIA S, ROSSI D, ROCCATELLO D: Interleukin 6 blockade as steroid-sparing treatment for 2 patients with giant cell arteritis. *J Rheumatol* 2011; 38: 2080-1.
94. SALVARANI C, MAGNANI L, CATANOSO M *et al*.: Tocilizumab: a novel therapy for patients with large-vessel vasculitis. *Rheumatology* (Oxford) 2012; 51: 151-6.
95. BHATIA A, ELL PJ, EDWARDS JC: Anti-CD20 monoclonal antibody (rituximab) as an adjunct in the treatment of giant cell arteritis. *Ann Rheum Dis* 2005; 64: 1099-100.
96. MAYRBAEURL B, HINTERREITER M, BURGSTALLER S, WINDPESSL M, THALER J: The first case of a patient with neutropenia and giant-cell arteritis treated with rituximab. *Clin Rheumatol* 2007; 26: 1597-8.
97. HOYER BF, MUMTAZ IM, LODDENKEMPER K *et al*.: Takayasu arteritis is characterised by disturbances of B cell homeostasis and responds to B cell depletion therapy with rituximab. *Ann Rheum Dis* 2012; 71: 75-9.
98. MORAGA, SICILIA JJ, BLANCO J, UBEDA I: Giant cell arteritis and renal amyloidosis: report of a case. *Clin Nephrol* 2001; 56: 402-6.
99. VOLTARELLI JC, OLIVEIRA MC, STRACIERI AB *et al*.: Haematopoietic stem cell transplantation for refractory Takayasu's arteritis. *Rheumatology* (Oxford) 2004; 43: 1308-9.
100. KOTTER I, DAIKELER T, AMBERGER C, TYNDALL A, KANZ L: Autologous stem cell transplantation of treatment-resistant systemic vasculitis – a single center experience and review of the literature. *Clin Nephrol* 2005; 64: 485-9.
101. DAIKELER T, KOTTER I, BOCELLI TYNDALL C *et al*.: Haematopoietic stem cell transplantation for vasculitis including Behçet's disease and polychondritis: a retrospective analysis of patients recorded in the European Bone Marrow Transplantation and European League Against Rheumatism databases and a review of the literature. *Ann Rheum Dis* 2007; 66: 202-7.
102. ARNAUD L, HAROCHE J, LIMAL N *et al*.: Takayasu arteritis in France: a single-center retrospective study of 82 cases comparing white, North African, and black patients. *Medicine* 2010; 89: 1-17.
103. BICAKCIGIL M, AKSU K, KAMALI S *et al*.: Takayasu's arteritis in Turkey – clinical and angiographic features of 248 patients. *Clin Exp Rheumatol* 2009; 27: S59-64.
104. PARK MC, LEE SW, PARK YB, CHUNG NS, LEE SK: Clinical characteristics and outcomes of Takayasu's arteritis: analysis of 108 patients using standardized criteria for diagnosis, activity assessment, and angiographic classification. *Scand J Rheumatol* 2005; 34: 284-92.
105. SATO EI, LIMA DN, ESPIRITO SANTO B, HATA F: Takayasu arteritis. Treatment and prognosis in a university center in Brazil. *Int J Cardiol* 2000; 75 (Suppl. 1): S163-6.
106. MAHR AD, JOVER JA, SPIERA RF *et al*.: Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum* 2007; 56: 2789-97.
107. MARTINEZ-LADO L, CALVINO-DIAZ C, PINEIRO A *et al*.: Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. *Medicine* 2011; 90: 186-93.
108. LEE JL, NAGUWA SM, CHEEMA GS, GERSHWIN ME: The geo-epidemiology of temporal (giant cell) arteritis. *Clinical Rev Allergy Immunol* 2008; 35: 88-95.
109. WATTS R, AL-TAIAR A, MOONEY J, SCOTT D, MACGREGOR A: The epidemiology of Takayasu arteritis in the UK. *Rheumatology* (Oxford) 2009; 48: 1008-11.
110. PAGNOUX C, MAHR A, HAMIDOU MA *et al*.: Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *New Engl J Med* 2008; 359: 2790-803.
111. REINHOLD-KELLER E, DE GROOT K: Use of methotrexate in ANCA-associated vasculitides. *Clin Exp Rheumatol* 2010; 28: S178-82.
112. DE GROOT K, MUHLER M, REINHOLD-KELLER E, PAULSEN J, GROSS WL: Induction of remission in Wegener's granulomatosis with low dose methotrexate. *J Rheumatol* 1998; 25: 492-5.
113. BRAUN J, KASTNER P, FLAXENBERG P *et al*.: Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008; 58: 73-81.
114. HOEKSTRA M, HAAGSMA C, NEEF C, PROOST J, KNUIF A, VAN DE LAAR M: Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. *J Rheumatol* 2004; 31: 645-8.
115. SALVARANI C, PIPITONE N: Treatment of large-vessel vasculitis: where do we stand? *Clin Exp Rheumatol* 2011; 29: S3-5.
116. SPIES CM, BURMESTER GR, BUTTGEREIT F: Methotrexate treatment in large vessel vasculitis and polymyalgia rheumatica. *Clin Exp Rheumatol* 2010; 28: S172-7.
117. HOUSSIAU FA, D'CRUZ D, SANGLE S *et al*.: Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis* 2010; 69: 2083-9.
118. GINZLER E, SHARON E, DIAMOND H, KAPLAN D: Long-term maintenance therapy with azathioprine in systemic lupus erythematosus. *Arthritis Rheum* 1975; 18: 27-34.
119. YAZICI H, PAZARLI H, BARNES CG *et al*.: A controlled trial of azathioprine in Behcet's syndrome. *New Engl J Med* 1990; 322: 281-5.
120. HAMURYUDAN V, OZYAZGAN Y, HIZLI N *et al*.: Azathioprine in Behçet's syndrome: effects on long-term prognosis. *Arthritis Rheum* 1997; 40: 769-74.
121. LANGFORD CA: Cyclophosphamide as induction therapy for Wegener's granulomatosis and microscopic polyangiitis. *Clin Exp Immunol* 2011; 164 (Suppl. 1): 31-4.
122. HATEMI G, SILMAN A, BANG D *et al*.: EULAR recommendations for the management of Behcet disease. *Ann Rheum Dis* 2008; 67: 1656-62.
123. AUSTIN HA, 3RD, KLIPPEL JH, BALOW JE *et al*.: Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *New Engl J Med* 1986; 314: 614-9.
124. HOUSSIAU FA, VASCONCELOS C, D'CRUZ D *et al*.: The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 2010; 69: 61-4.
125. HOUSSIAU FA, D'CRUZ DP, HAGA HJ, HUGHES GR: Short course of weekly low-dose intravenous pulse cyclophosphamide in the treatment of lupus nephritis: a preliminary study. *Lupus* 1991; 1: 31-5.
126. RADIS CD, KAHL LE, BAKER GL *et al*.:Effects of cyclophosphamide on the development of malignancy and on long-term survival of patients with rheumatoid arthritis. A 20-year follow-up study. *Arthritis Rheum* 1995; 38: 1120-7.
127. TYNJALA P, LINDAHL P, HONKANEN V, LAHDENNE P, KOTANIEMI K: Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis* 2007; 66: 548-50.
128. TARKIAINEN M, TYNJALA P, VAHASALO P, LAHDENNE P: Occurrence of inflammatory bowel disease in four patients with juvenile idiopathic arthritis receiving etanercept or infliximab. *Scand J Rheumatol* 2011; 40: 150-2.
129. ROSENSTIEL P, AGNHOLT J, KELSEN J *et al*.: Differential modulation of p38 mitogen activated protein kinase and STAT3 signalling pathways by infliximab and etanercept in intestinal T cells from patients with Crohn's disease. *Gut* 2005; 54: 314-5; author reply 6-6.
130. LUQMANI R: Treatment of polymyalgia rheumatica and giant cell arteritis: are we any further forward? *Ann Intern Med* 2007; 146: 674-6.
131. FIELD M, COOK A, GALLAGHER G: Immuno-localisation of tumour necrosis factor and its receptors in temporal arteritis. *Rheumatology Int* 1997; 17: 113-8.
132. WEYAND CM, GORONZY JJ: Medium- and large-vessel vasculitis. *New Engl J Med* 2003; 349: 160-9.
133. AYDIN SZ, YILMAZ N, AKAR S *et al*.: Assessment of disease activity and progression in Takayasu's arteritis with Disease Extent Index-Takayasu. *Rheumatology* (Oxford) 2010; 49: 1889-93.