EXTENDED REPORT

Tumour necrosis factor α blocking agents in refractory adult Still's disease: an observational study of 20 cases

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Ann Rheum Dis 2005;**64**:262–266. doi: 10.1136/ard.2004.024026

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Accepted 1 June 2004

Background: Consensus is lacking on treatment for corticosteroid resistant adult onset Still's disease (ASD).
Objective: To assess anti-TNFα efficacy and tolerance in refractory ASD.
Methods: All departments of rheumatology and internal medicine in France were contacted by mail to identify cases of refractory ASD for which anti-TNFα had been used. Medical information was collected using a standardised questionnaire.
Results: Of 20 patients with mean age 40.7 years (range 18–74) at treatment start and mean disease duration 8.5 years (range 2–21), the clinical expression of ASD was predominantly systemic in five patients and polyarticular in 15. Response to corticosteroids and methotrexate had been considered inadequate in all patients. Infliximab was used to treat 15 patients, and etanercept used for 10; five had received both drugs consecutively. Steroids were concurrently used in 18 patients and an immunosuppressant in 17. At a mean (SD) follow up of 13 (14) months, complete remission had occurred in five cases (of 25 treatment sequences): one receiving etanercept and four infliximab. Partial response was observed in 16 cases (seven etanercept and nine infliximab). Treatment failed in four cases (two with each anti-TNFα). At the last visit, anti-TNFα therapy was discontinued in 17 cases, 11 times because of lack (or loss) of efficacy, four times because of a side effect, and twice for other reasons.
Conclusion: Anti-TNFα therapy may be helpful for some patients with refractory ASD. However, most patients achieve only partial remission. Additional information is thus needed to evaluate more precisely the risk–benefit ratio of this treatment.

Adult onset Still's disease (ASD) is a rare condition, prevalence of which is estimated to be 1.5 cases per 100 000 to 1.5 cases per 1 000 000.[1–3] Its expression is very polymorphic and its progression highly variable.[4–8] Although some patients have a unique flare without any recurrence, most have recurrences, which progress to a chronic form of the disease.[9] The literature distinguishes two main chronic forms: a systemic form with fever, asthenia, and other general symptoms, and an arthritic form with polyarthritis, which is sometimes erosive.[4–7 9–11]

Because of its low prevalence and its heterogeneous expression, randomised controlled trials are difficult to perform in ASD patients. Thus, all available evidence concerning effective therapies has emerged from open label studies. Aspirin and other non-steroidal anti-inflammatory drugs have been found to stabilise the disease in only 10–30% of patients.[6 8 11] In fact, corticosteroids are the preferred treatment, resulting in a clinical response in 76–95% of patients.[4 8 10–13] However, dependence on or resistance to steroids is common, and other treatments are needed. By homology with rheumatoid arthritis, several disease modifying antirheumatic drugs (DMARDs), including gold salts, hydroxychloroquine, D-penicillamine, sulfasalazine, and cyclophosphamide, have been tested.[4 9–12 14 15] More recently, two other treatments have been found to be effective in cases of steroid dependence or resistance: methotrexate[16–19] and polyvalent intravenous immunoglobulin (IV Ig).[20–22] As several immunological studies have previously shown that Th-1 cytokines, specifically TNFα, are involved in ASD pathogenesis, anti-TNFα agents, which are highly efficient in rheumatoid arthritis and ankylosing spondylitis,[23 24] have been also evaluated in ASD. Apart from reports of a few isolated cases, only the results of three open label studies have been published.[25–28] Two studies were retrospective and included five and six patients respectively, treated with either etanercept or infliximab.[26 27] The other study was a prospective open label trial of 12 patients with established ASD treated with etanercept.[28] Thus, complete and partial remission might be achieved with anti-TNFα therapy in some subsets of patients.

The Club Rhumatismes and Inflammation, a section of the French Society of Rheumatology dedicated to the study of inflammatory rheumatisms, organised a survey in French hospitals to retrospectively evaluate the efficacy and tolerance of anti-TNFα in the treatment of ASD.

MATERIALS AND METHODS

Patient identification

This retrospective study was based on a national postal survey of the departments of rheumatology and internal medicine in all French hospitals; general or teaching. Departments that had treated patients with established ASD, according to Yamaguchi classification criteria,[29] who were resistant to conventional DMARD therapy, for whom anti-TNFα therapy had been tested, were sent a standardised questionnaire asking about age and symptoms at ASD diagnosis, classification criteria, treatments tested before anti-TNFα therapy, and items related to the therapy.

Anti-TNFα therapy

At the time of the survey, only etanercept and infliximab were available in France. Patients receiving either drug were eligible, whatever the therapeutic scheme. The dose and mode of administration were those usually used in rheumatoid arthritis (3 mg/kg infusion of infliximab administered at weeks 0, 2, 6, 10, and every 8 weeks thereafter, and 25 mg etanercept administered subcutaneously twice a week). The

Abbreviations: ASD, adult onset Still's disease; DMARD, disease modifying antirheumatic drug; MRI, magnetic resonance imagiing

study required no minimal duration of treatment, and all patients having received at least one injection or infusion were included.

Efficacy and tolerance of anti-TNFα therapy

The symptoms and circumstances having led to anti-TNFα therapy were recorded. The response to anti-TNFα was defined in three categories on the basis of the opinion of the physician in charge of the patient: remission was defined as a complete resolution of all clinical and biological ASD related symptoms, except joint erosion; failure was defined as an absence of significant improvement within 1−3 months following treatment start; and partial remission was defined as the persistence of one or several ASD related symptoms. In the latter case, the remaining symptoms were recorded. In the case of therapy discontinuation, the reason for discontinuation was recorded. All side effects, either suspected or certain, were also noted.

RESULTS

The survey identified 20 ASD patients in 12 different rheumatology or internal medicine departments. The mean age was 32.2 (19) years (median 28 years) at ASD diagnosis and 40.7 (17) years (median 34.5 years) at anti-TNFα therapy start (table 1). The ratio of males to females was 1 to 4 (5 men, 15 women). All patients satisfied Yamaguchi criteria for ASD.[29] Any other differential diagnoses had been ruled out. In four patients, the disease began during childhood, and the patients had active disease up to the adult age. At the time of anti-TNFα therapy, all patients were adult. Mean disease duration at therapy start was 8.5 (6) years (median 6.5 years, range 2–21 years). In five patients, the disease was predominantly systemic (mainly fever, arthralgia, and rashes); in 15, chronic polyarthritis was the dominant feature. All patients had had several treatments (table 1), especially prednisone and methotrexate, before anti-TNFα therapy.

All patients had refractory active disease at the start of anti-TNFα therapy (table 2). Ten received infliximab only and five etanercept only. In five cases, patients were successively treated by both drugs: four received etanercept first, then infliximab because of lost efficacy; one received the reverse sequence after experiencing a systemic anaphylactic reaction after the third infliximab infusion. All but two patients received anti-TNFα in association with oral prednisone. Six patients receiving etanercept also took another DMARD (four methotrexate, one azathioprine, and one IV Ig) and 14 receiving infliximab took another DMARD (12 methotrexate, two azathioprine). The mean treatment duration was 11 (9) months for etanercept and 9 (7) months for infliximab.

The mean follow up was 13 months for etanercept and 14 for infliximab (median 9 and 10 months, respectively) (table 3). Anti-TNFα efficacy was discernable within 2−6 weeks following treatment start. Complete remission was observed in only five patients (one treated with etanercept and four with infliximab). Most patients achieved a partial remission: 16 of 25 treatments (7/10 receiving etanercept and 9/15 infliximab). One patient had a partial and dissociated response to etanercept: all symptoms but fever improved. After a few months, a global flare occurred and etanercept was discontinued. Finally, failure to respond to anti-TNFα therapy was noted in four patients. Both forms of the disease seemed to have similar response patterns to therapy. Partial remission was achieved in 80% of patients (4/5 systemic; 12/15 articular ASD).

Five patients switched etanercept and infliximab treatment: four received first etanercept then infliximab, and one had the reverse combination (fig 1). In all cases, the switch was made because the first anti-TNFα was ineffective; one case had concomitant skin rash, which accelerated the discontinuation of infliximab. In all but two cases, the alternative agent produced an insufficient response, and after a mean follow up of 6 months, the second agent was discontinued. One patient had a skin rash that led to etanercept discontinuation. Another case had an accidental serious burn of the upper limbs that required infliximab discontinuation, despite a partial but significant response of ASD.

At the last follow up, the agents had been discontinued in 17/25 treatment sequences (7/10 etanercept, 10/15 infliximab; table 4), the main reason being a lack of efficacy. Side effects were responsible for discontinuation in three patients. One patient had a skin rash and blurred vision, and received a diagnosis of optic neuritis. Antinuclear antibodies were present at a titre of 1/80, without any reactivity for double stranded DNA, soluble antigens, or histons, and the skin biopsy suggested an allergic origin (no lupus band on immunofluorescence analysis). Brain magnetic resonance imaging (MRI) and angio-MRI results were normal, as was visual evoked potential. With discontinuation of infliximab, all symptoms resolved within 6 months. A 74 year old woman died of cardiac failure 2 weeks after the second infliximab infusion. She had had one episode of pericarditis and arrhythmia when ASD was diagnosed 2 years before anti-TNFα therapy, but had had no other cardiac symptoms during the course of the disease. After the second infusion,

Table 1 Summary of patient characteristics

Characteristic	
Age at ASD diagnosis	
Mean (SD) (range)	32.2 (19) (11 to 72)
Median	28
Childhood onset (no.)	4
Disease free interval between childhood and adult symptoms	1
Disease duration (years)	
Mean (SD) (range)	8.5 (6) (2 to 21)
Median	6.5
Age at anti-TNF start (years)	
Mean (SD) (range)	40.7 (17) (18 to 74)
Median	34.5
Predominant clinical expression	
Chronic arthritis	15
Systemic	5
Symptoms (no.)	
Fever	20
Arthralgia	20
Polyarthritis	18
Sore throat/pharyngitis	14
Rash	16
Seritis	4
Lymphadenopathy	6
Increased leukocyte level	20
Polymorphonuclear level >10 000 mm^3	20
Abnormal liver function test result	6
High serum ferritin level	14
Disseminated intravascular coagulation syndrome	5
Previous treatments	
Prednisone	20
Methotrexate	20
Intravenous polyvalent immunoglobulin	5
Sulfasalazine	2
Hydroxychloroquine	6
Gold salts	2
D-Penicillamin	1
Thalidomide	1
Cyclosporine A	5
Cyclophosphamide	4
Azathioprine	3

Table 2 Patients' outcome under anti-TNF alpha therapy

No.	Sex	Main clinical expression	ASD duration (years)	Age	Main symptoms	Therapy Type	Associated drug	Response	Remaining symptoms	Follow up
1	F	Systemic	2	33	Fever, arthralgia, rash	Etanercept 25 mg ×2/week	PDN 80 mg/day	Remission	None	5 months. Anti-TNF stopped (other: drug availability)
2	F	Articular	5	55	Fever, polyarthritis, rash	Etanercept 25 mg ×2/week	AZA 100 mg/day PDN 30 mg/day	Partial response	Isolated fever	12 months. Anti-TNF stopped (lack of efficacy)
						Infliximab 5 mg/kg	AZA 100 mg/day MethylPDN 1g PDN 30 mg/day	Partial response	Isolated fever	10 months. Anti-TNF stopped (lack of efficacy)
3	M	Articular	7	55	Polyarthritis	Etanercept 25 mg ×2/week	IV Ig[1]	Failure	Polyarthritis	3 months. Anti-TNF stopped (lack of efficacy)
4	F	Articular	5	36	Fever, polyarthritis, fatigue	Etanercept 25 mg ×2/week	PDN 20 mg/day	Partial response	Oligoarthritis	43 months. Anti-TNF ongoing
5	F	Articular	17	29	Polyarthritis	Infliximab 3 mg/kg	MTX	Failure	Polyarthritis	1 month. Anti-TNF stopped (side effects)
6	F	Systemic	2	74	Fever, arthralgia, rash	Infliximab 5 mg/kg	PDN 20 mg/day MTX 15 mg/week	Partial response	Rash, arthralgia	1 month. Anti-TNF stopped (side effects)
7	M	Articular	17	28	Fever, polyarthritis, myalgia	Infliximab 3 mg/kg	PDN 40 mg/day MTX 7.5 mg/week	Failure	Fever, arthritis, myalgia Polyarthritis, myalgia	2 months. Anti-TNF stopped (side effects)
					Rash	Etanercept 25 mg ×2/week	PDN 40 mg/day MTX 7.5 mg/week	Partial response	Rash, arthralgia	1 month. Anti-TNF stopped (side effects)
8	F	Articular	6	61	Polyarthritis, rash	Infliximab 3 mg/kg	PDN 10 mg/day MTX 17.5 mg/week	Remission	None	44 months. Anti-TNF ongoing
9	F	Articular	4	44	Polyarthritis	Infliximab 3 mg/kg	PDN 50 mg/day MTX 15 mg/week	Partial response	Few arthritis	34 months. Anti-TNF ongoing
10	F	Systemic	2	73	Fever, arthralgia, fatigue	Infliximab 3 mg/kg	PDN MTX 15 mg/week	Partial response	Arthralgia, fatigue	12 months. Anti-TNF stopped (lack of efficacy)
11	F	Articular	21	32	Fever, polyarthritis, rash	Etanercept 25 mg ×2/week	PDN 15 mg/day MTX 7.5 mg/week	Partial response	Few arthritis	10 months. Anti-TNF stopped (lack of efficacy)
						Infliximab 3 mg/kg	PDN 12 mg/day MTX 7.5 mg/week	Partial response	Few arthritis	7 months. Anti-TNF stopped (lack of efficacy)
12	M	Articular	12	29	Fever, polyarthritis, rash	Infliximab 3 mg/kg	MTX 15 mg/week	Remission	None	12 months. Anti-TNF stopped(lack of efficacy)
13	F	Articular	2	18	Polyarthritis	Etanercept	PDN 10 mg/day	Partial response	Few arthritis	35 months. Anti-TNF ongoing
					Fatigue	25 mg ×2/week	MTX 10 mg/week			
14	M	Articular	3	25	Polyarthritis, rash	Infliximab 3 mg/kg	PDN 10 mg/day MTX 15 mg/week	Remission	None	16 months. Anti-TNF ongoing
15	F	Articular	12	29	Fever, arthralgia	Infliximab 3 mg/kg	PDN 5 mg/day MTX 12.5 mg/week	Remission	None	36 months. Anti-TNF ongoing
16	F	Systemic	14	37	Fever, arthralgia, rash	Infliximab 3 mg/kg	PDN 20 mg/day AZA 150 mg/day	Partial response	Arthralgia, rash	9 months. Anti-TNF stopped (lack of efficacy)
17	M	Articular	5	18	Fever, polyarthritis	Etanercept 25 mg ×2/week	PDN 20 mg/day	Partial response	Few arthritis	9 months. Anti-TNF stopped (lack of efficacy)
						Infliximab 3 mg/kg	PDN 15–20 mg/day MT X 7.5 mg/week	Partial response	Few arthritis	3 months. Anti-TNF ongoing (lack of efficacy)
18	F	Articular	11	46	Fever, polyarthritis	Etanercept 25 mg ×2/week	PDN 15– 20 mg/day MTX 20 mg/week	Partial response	Few arthritis	6 months. Anti-TNF ongoing
19	F	Systemic	7	32	Fever, polyarthritis, rash	Etanercept 25 mg ×2/week	PDN 15– 20 mg/day	Failure	Fever, arthritis, rash	3 months, Anti-TNF stopped (lack of efficacy)
					Sore throat	Infliximab 3 mg/kg	PDN 15– 20 mg/day	Partial response	Few arthritis, rash	4 months. Anti-TNF stopped (other: serious burn)
20	F	Articular	15	60	Fever, polyarthritis, rash	Infliximab 3 mg/kg	PDN 45 mg/day MTX 17.5 mg/week	Partial response	Few arthritis	8 months. Anti-TNF ongoing

PDN, prednisone; AZA, azathioprine; MethylPDN, methylprednisolone; IV Ig, intravenous polyvalent immunoglobulin; MTX, methotrexate.

Table 3 Treatment response

	All treatments (n = 25)*	Etanercept (n = 10)	Infliximab (n = 15)
Treatment duration (months)			
Mean (SD)	13 (14)	13 (14)	14 (14)
Median	9	9	10
Range	1 to 44	1 to 43	1 to 44
Response to therapy			
Complete remission	5	1	4
Partial response	16	7	9
Failure	4	2	2

*A total of 25 treatments in 20 patients were analysable. 10 patients received etanercept, 15 infliximab, and 5 both drugs.

she developed high fever (39°C) and features of refractory cardiac failure, the exact origin remaining unknown. The third patient discontinued both infliximab and etanercept because of an allergic skin reaction.

Mild side effects were observed in seven patients (table 5). Three patients had skin rashes, which responded to antihistamine treatments. Serious side effects occurred in two patients. One had recurrent bronchitis and an episode of pneumonia requiring antibiotics. However, it was possible to maintain therapy with only minor changes in the infliximab infusion periodicity. Another case had a spontaneous thigh abscess. Antibiotics and etanercept discontinuation resolved the abscess without need for surgical intervention; anti-TNFα therapy was reintroduced within 2 months, without further infection.

DISCUSSION

Compared with previously published papers, the present series brings additional relevant data on the efficacy of anti-TNFα agents in refractory ASD, thanks to the number of patients, the presence of both systemic or articular forms of the disease, the use of either infliximab, etanercept, or both, and a rather long follow-up (13 months; up to 44 months for some patients). The retrospective design of our study is a limitation, but prospective randomised control trials are difficult to conduct for ASD. This limitation is shared by most of the studies published so far,[25–27] which included only a few patients, six at maximum. Only one series, of 12 cases, used a prospective, open label design and reported the efficacy of etanercept in patients with a polyarticular form of ASD.[28]

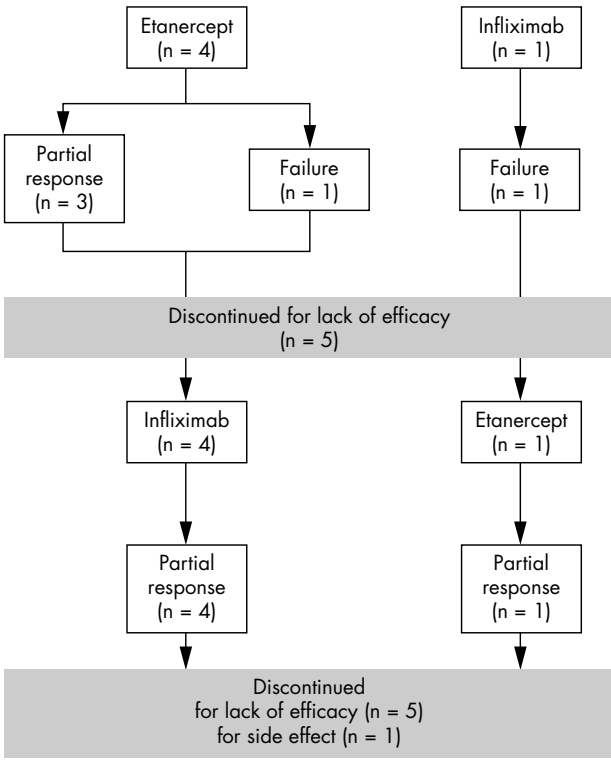

Figure 1 Breakdown of the five patients with anti-TNFα switches.

Table 4 Anti-TNFα discontinuation

	Both treatments (n = 25)	Etanercept (n = 10)	Infliximab (n = 15)
Discontinuation	17	7	10
Lack of efficacy	11	5	6
Side effect	4	1	3
Other	2	1	1

As our study was retrospective and collected data from all over France, we tried to homogenise the information by defining three clinical responses based on physicians' opinions. With use of this classification, we found that when anti-TNFα agents were efficacious, clinical improvement occurred rapidly, within the first month of treatment. Complete remission was possible under both agents but was rare, only 5/20 cases, which is consistent with data from the literature.[26 28] Partial response was observed in most patients (16/25 cases) in our series as well as in those of the literature. Only one patient experienced a remission of joint and skin symptoms without any substantial change in fever spikes. Such a dissociation had already been mentioned in ASD with use of other DMARDs[16] and etanercept.[28] The patients with a systemic form of ASD seemed to respond the same as the patients with an articular form of the disease.

The present series offers information about the efficacy of switching from one anti-TNFα to the other. In opposition to what has already been suggested for rheumatoid arthritis,[30] such a switch did not seem to be efficacious in ASD. Two patients in whom therapy with one anti-TNFα failed showed partial response to the other; however, the response was transient and led to rapid discontinuation of the second agent. For the three other cases, a partial and transient response was observed with use of both drugs. The pathogenic basis of such occurrences is unknown. In general, the safety of anti-TNFα therapy was in accordance with what has been described for rheumatoid arthritis, psoriasitic arthritis, ankylosing spondylitis, or inflammatory enterocolitis.[31–33] We did not observe any cases of tuberculosis, which is probably explained by the large diffusion of warnings from pharmaceutical firms or governmental agencies at the time of

Table 5 Side effects reported under anti-TNF alpha therapy

	Both treatments (n = 25)	Etanercept (n = 10)	Infliximab (n = 15)
Rash	5	3	2
Infections	2	1 (recurrent bronchitis)	1 (thigh abscess)
Other	2	2 (1 lupus rash + optic neuritis; 1 cardiac failure)	0

the study. Other infectious side effects, noted in the literature,[27] were found in our series; no life threatening infection was recorded. Skin rashes were observed in our patients but were distinguishable from ASD specific skin lesions: they were pruritic urticarian lesions occurring soon after anti-TNFα injection or infusion, and had no vesperal timing and relation to fever spikes. The most serious side effect was an anti-TNFα induced autoimmune reaction in one patient, who had a skin rash and optic neuritis. Such events have been reported after anti-TNFα therapy in patients with other inflammatory conditions.[34–36] In general, therapy discontinuation resolved the symptoms.

In conclusion, anti-TNFα agents may be useful in the treatment of refractory ASD. However, this therapy does not seem to be as efficacious in ASD as in rheumatoid arthritis or spondylarthropathies.

ACKNOWLEDGEMENTS

The authors want to acknowledge the physicians who provided the 20 observations: Professor M Alcalay, Rheumatology, La Mileterie Hospital, Poitiers; Professor Z Amoura, Internal Medicine, Pitie-Salpetriere University Hospital, Paris; Dr S Berthier, Internal Medicine, Le Bocage Hospital, Dijon; Dr F Bonnet, Internal Medicine, University Hospital, Bordeaux; Dr C Dumoulin, Rheumatology, Pellegrin Hospital, Bordeaux; Professor P Gaudin, Rheumatology, A Michallon Hospital, Grenoble; Dr J-E Gottenberg, Rheumatology, Cochin Hospital, Paris; Dr L Lequen, Rheumatology, General Hospital, Pau; Professor P Mercié, Internal Medicine, Saint-Andre Hospital, Bordeaux; Dr B Moura, Rheumatology, Ambroise Paré Hospital, Boulogne; Dr X Puéchal, General Hospital, Le Mans; Professor A Saraux, Rheumatology, La Cavale Blanche Hospital, Brest; Dr S Schrambach, Haute-Pierre Hospital, Strasbourg; Dr J-F Viallard, Internal Medicine, Haut-Leveque Hospital, Bordeaux.

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The study was funded by the The Club Rhumatismes and Inflammation (CRI) section of the French Society of Rheumatology.

REFERENCES

1 **Bywaters EG**. Still's disease in the adult. *Ann Rheum Dis* 1971;**30**:121–33.
2 **Magadur-Joly G**, Billaud E, Barrier JH, Pennec YL, Masson C, Renou P, *et al*. Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. *Ann Rheum Dis* 1995;**54**:587–90.
3 **Wakai K**, Ohta A, Tamakoshi A, Ohno Y, Kawamura T, Aoki R, *et al*. Estimated prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological survey in Japan. *J Epidemiol* 1997;**7**:221–5.
4 **Reginato AJ**, Schumacher HR Jr, Baker DG, CR OC, Ferreiros J.. Adult onset Still's disease: experience in 23 patients and literature review with emphasis on organ failure. *Semin Arthritis Rheum* 1987;**17**:39–57.
5 **Ohta A**, Yamaguchi M, Tsunematsu T, Kasukawa R, Mizushima H, Kashiwagi H, *et al*. Adult Still's disease: a multicenter survey of Japanese patients. *J Rheumatol* 1990;**17**:1058–63.
6 **Pouchot J**, Sampalis JS, Beaudet F, Carette S, Decary F, Salusinsky-Sternbach M, *et al*. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine (Baltimore)* 1991;**70**:118–36.
7 **Masson C**, Le Loet X, Liote F, Renou P, Dubost JJ, Boissier MC, *et al*. Adult Still's disease: part I. Manifestations and complications in sixty-five cases in France. *Rev Rhum Engl Ed* 1995;**62**:748–57.
8 **Masson C**, Le Loet X, Liote F, Renou P, Dubost JJ, Boissier MC, *et al*. Adult Still's disease. Part II. Management, outcome, and prognostic factors. *Rev Rhum Engl Ed* 1995;**62**:758–65.
9 **Ohta A**, Yamaguchi M, Kaneoka H, Nagayoshi T, Hiida M. Adult Still's disease: review of 228 cases from the literature. *J Rheumatol* 1987;**14**:1139–46.
10 **Wouters JM**, van de Putte LB. Adult-onset Still's disease; clinical and laboratory features, treatment and progress of 45 cases. *Q J Med* 1986;**61**:1055–65.
11 **Cush JJ**, Medsger TA Jr, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. Clinical course and outcome. *Arthritis Rheum* 1987;**30**:186–94.
12 **Khraishi M**, Fam AG. Treatment of fulminant adult Still's disease with intravenous pulse methylprednisolone therapy. *J Rheumatol* 1991;**18**:1088–90.
13 **Bisagni-Faure A**, Job-Deslandre C, Menkes CJ. Intravenous methylprednisolone pulse therapy in Still's disease. *J Rheumatol* 1992;**19**:1487–8.
14 **Marchesoni A**, Ceravolo GP, Battafarano N, Rossetti A, Tosi S, Fantini F. Cyclosporin A in the treatment of adult onset Still's disease. *J Rheumatol* 1997;**24**:1582–7.
15 **Shojania K**, Chalmers A, Rangno K. Cyclosporin A in the treatment of adult Still's disease. *J Rheumatol* 1995;**22**:1391–2.
16 **Kraus A**, Alarcon-Segovia D. Fever in adult onset Still's disease. Response to methotrexate. *J Rheumatol* 1991;**18**:918–20.
17 **Aydintug AO**, D DC, Cervera R, Khamashta MA, Hughes GR. Low dose methotrexate treatment in adult Still's disease. *J Rheumatol* 1992;**19**:431–5.
18 **Fujii T**, Akizuki M, Kameda H, Matsumura M, Hirakata M, Yoshida T, *et al*. Methotrexate treatment in patients with adult onset Still's disease—retrospective study of 13 Japanese cases. *Ann Rheum Dis* 1997;**56**:144–8.
19 **Fautrel B**, Borget C, Rozenberg S, Meyer O, Le Loet X, Masson C, *et al*. Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease. *J Rheumatol* 1999;**26**:373–8.
20 **Permal S**, Wechsler B, Cabane J, Perrot S, Blum L, Imbert JC. Treatment of Still disease in adults with intravenous immunoglobulins. *Rev Med Interne* 1995;**16**:250–4.
21 **Vignes S**, Wechsler B, Amoura Z, Papo T, Frances C, Huong DL, *et al*. Intravenous immunoglobulin in adult Still's disease refractory to non-steroidal anti-inflammatory drugs. *Clin Exp Rheumatol* 1998;**16**:295–8.
22 **Vignes S**, Le Moel G, Fautrel B, Wechsler B, Godeau P, Piette JC. Percentage of glycosylated serum ferritin remains low throughout the course of adult onset Still's disease. *Ann Rheum Dis* 2000;**59**:347–50.
23 **Furst DE**, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Dougados M, *et al*. Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other immune mediated inflammatory diseases. *Ann Rheum Dis* 2003;**62**:2–9.
24 **Blumenauer B**, Judd M, Wells G, Burls A, Cranney A, Hochberg M, *et al*. Infliximab for the treatment of rheumatoid arthritis. *Cochrane Database Syst Rev*, 2002;CD003785..
25 **Cavagna L**, Caporali R, Epis O, Bobbio-Pallavicini F, Montecucco C. Infliximab in the treatment of adult Still's disease refractory to conventional therapy. *Clin Exp Rheumatol* 2001;**19**:329–32.
26 **Kraetsch HG**, Antoni C, Kalden JR, Manger B. Successful treatment of a small cohort of patients with adult onset of Still's disease with infliximab: first experiences. *Ann Rheum Dis* 2001;**60**:55–7.
27 **Tamesis ER**, Reginato AM, Hubscher O, Reginato AJ. Etanercept in recalcitrant adult onset Still's disease. *Arthritis Rheum* 2000;**43**:S229.
28 **Husni ME**, Maier AL, Mease PJ, Overman SS, Fraser P, Gravallese EM, *et al*. Etanercept in the treatment of adult patients with Still's disease. *Arthritis Rheum* 2002;**46**:1171–6.
29 **Yamaguchi M**, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, *et al*. Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992;**19**:424–30.
30 **Buch MH**, Bingham SJ, Bejarano V, White J, Emery P. Do patients with rheumatoid arthritis demonstrate an improvement on etanercept following an inadequate response to infliximab. *Arthritis Rheum* 2003;**48**:S325.
31 **Antoni C**, Braun J. Side effects of anti-TNF therapy: current knowledge. *Clin Exp Rheumatol* 2002;**20**:S152–7.
32 **Criscione LG**, St Clair EW. Tumor necrosis factor-alpha antagonists for the treatment of rheumatic diseases. *Curr Opin Rheumatol* 2002;**14**:204–11.
33 **Fleischmann R**, Iqbal I, Nandeshwar P, Quiceno A. Safety and efficacy of disease-modifying anti-rheumatic agents: focus on the benefits and risks of etanercept. *Drug Saf* 2002;**25**:173–97.
34 **Foroozan R**, Buono LM, Sergott RC, Savino PJ. Retrobulbar optic neuritis associated with infliximab. *Arch Ophthalmol* 2002;**120**:985–7.
35 **Debandt M**, Vittecoq O, Descamps V, Le Loet X, Meyer O. Anti-TNF-alpha-induced systemic lupus syndrome. *Clin Rheumatol* 2003;**22**:56–61.
36 **Shakoor N**, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002;**359**:579–80.