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# **Infliximab treatment in patients with rheumatoid arthritis and spondyloarthropathies in one rheumatological centre; two years' drug survival**

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**Abstract** The aim of the present study was to determine the drug survival during two years' follow-up in patients (n=104) with active rheumatoid arthritis (RA) or spondyloarthropathy (SpA) who were treated with infliximab as their first biological anti-rheumatic drug in a single rheumatological centre. According to the national guidelines, infliximab was added to the treatment with combinations of traditional disease modifying anti-rheumatic drugs (DMARD). Patients' records were analyzed at baseline and after two years of follow-up. The response to treatment was determined inadequate if the response was lower than ACR50 (American College of Rheumatology 50) in RA or the reduction of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was lower than 50% or 2 cm in SpA. Drug survival in infliximab treated patients after two years was 40% and among those who continued with the therapy the prednisolone dose has been reduced by 52%. Discontinuation rate was 60% during two years of follow-up, where 7% achieved remission and 22% of the patients were regarded as poor responders. Twenty-four percent of the patients discontinued due to an adverse event, mainly infections and hypersensitivity reactions. Two drug related leukopenias were diagnosed. In the present study, infliximab therapy was initiated in RA or SpA patients who had active disease despite ongoing treatment with combinations of DMARDs. The drug survival with infliximab was 40% after two years of follow-up. Sixty per cent discontinued infliximab treatment during two years' follow-up, mainly due to unsatisfactory or waning efficacy or to a severe adverse event.

**Keywords**: infliximab, rheumatoid arthritis, spondyloarthropathies, adverse events

## **Introduction**

Tumor necrosis factor alpha (TNF $\alpha$ ) modulator infliximab has been shown to be effective, antierosive and well tolerated in the treatment of rheumatoid arthritis (RA) [1-4] and spondyloarthropathies (SpA) [5, 6] in clinical trials. It is routinely used in the everyday practice when traditional DMARDs are not sufficiently effective. Although infliximab is generally safe and well tolerated, sometimes the treatment must be discontinued due to adverse events [1-3, 6-10], mainly infections [11-14] and hypersensitivity reactions [14, 15]. In addition, inadequate or waning efficacy complicates drug survival in infliximab-treated patients [8, 10, 14, 16].

Many clinical trials use ACR20 as the criteria for continuation of infliximab treatment, while in Finland the criteria for continuation has been set as ACR50 or a better response [17]. According to the national guidelines [17], TNF $\alpha$  antagonist treatment is indicated if the patient is suffering from continuously active disease despite the treatment with combinations of traditional disease modifying antirheumatic drugs (DMARD), including methotrexate. In addition, a TNF $\alpha$  antagonist is usually added to the treatment with one or more DMARDs (see section "Patients and methods"). In the present study, our interest was to analyse data from patients with active and refractory RA or SpA in a single rheumatological centre, who received infliximab as their first biological treatment in combination with DMARDs on clinical grounds according to the national guidelines. We have recently published a six months' follow-up data, on RA and SpA patients receiving infliximab as their first biological drug, focusing on adverse events and other reasons for discontinuation of the treatment [18]. In the present study, we wanted to extend our analysis to drug survival up to two years in the same cohort. We defined the number of

patients who achieved at least 50% response and continued the treatment with infliximab, the number of patients who discontinued the treatment, and the reason for the discontinuation, and listed the adverse events leading to discontinuation of the treatment.

## **Patients and methods**

In the present study, 104 patients with active rheumatoid arthritis or spondyloarthropathy were treated with infliximab as their first biological treatment in the Department of Internal Medicine, Center for Rheumatic Diseases of the Tampere University Hospital, Finland. Indication commencement of infliximab treatment was based on the national recommendations [17]. The criteria to start infliximab treatment for RA was that the patient was suffering from continuously active RA [at least six swollen and tender joints, and additionally the duration of morning stiffness at least 45 min and / or erythrocyte sedimentation rate (ESR)  $\geq 30$  mmHg and / or serum C-reactive protein (CRP)  $\geq 28$  mg/l] despite treatment with combinations of traditional DMARDs including methotrexate and glucocorticoids [17]. In patients with ankylosing spondylitis (AS), the criteria to start infliximab treatment were: 1) inefficiency of at least two nonsteroidal anti-inflammatory drugs (NSAIDs) over at least three months, 2) sulphasalazine (methotrexate if sulphasalazine contraindicated) or possibly other DMARDs had been ineffective, and 3) the patient had an active disease based on BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) ( $\geq 4$  cm) and on clinical grounds [acute sacroiliitis, elevated acute phase reactants, magnetic resonance imaging (MRI) findings]. In the other spondyloarthropathies like psoriatic arthritis (PsA) or inflammatory bowel disease (IBD) associated arthritis, there were no defined criteria to start treatment with biologicals, but the decision was made on clinical grounds by an experienced rheumatologist based on the severity of arthritis and the inflammatory axial disease, and on criteria available for RA and SpA.

Infliximab was given intravenously at a dose of 3 mg/kg in weeks 0, 2, 6 and in every 8 weeks thereafter. The response determined whether the dose was elevated or lowered, or the infusion intervals shortened or lengthened. Infliximab was combined usually with methotrexate and in many cases with other DMARDs (mostly sulphasalazine or hydroxychloroquine) and low-dose prednisolone. The clinical response was carefully followed and registered by an experienced rheumatologist at each visit. In RA, the evaluation included ACR (American College of Rheumatology) response criteria [19] containing number of swollen and tender joints, the physician's assessment of disease activity (VAS, Visual Analog Scale, 0-10 cm), patient's assessment of general health (VAS), pain (VAS) and HAQ (Health Assessment Questionnaire), and markers of acute phase activity (ESR and CRP). A treatment response lower than ACR50 was regarded ineffective. In SpA, the clinical response included BASDAI and BASFI (Bath Ankylosing Spondylitis Functional Index) indexes, and the treatment was regarded ineffective if the reduction of BASDAI index was lower than 50% or less than 2 cm.

The drug treatment in addition to infliximab i.e. glucocorticoids, DMARDs and NSAIDs, was documented. In the case of withdrawal, the reason (adverse event, inefficiency, remission or other reasons) was registered, and cases in which a severe adverse event caused the discontinuation of the treatment were reported to National Agency of Medicines (NAM).

## Results

### *Patients*

In the present study, we analyzed drug survival in patients with active and refractory RA or SpA (n=104) treated with infliximab as their first biologic drug in the Center for Rheumatic Diseases, Tampere University Hospital during years 1999-2005. The mean age was 45 years (range 18-75), 64 patients (62%) were female and the mean disease duration was 12 years (range 0.8-52) (Table 1). One or more concomitant DMARDs in addition to infliximab were being used in 95% of the patients and 91% were receiving glucocorticoids in accordance to the national recommendations for infliximab treatment (Table 1). Sixty-two (60%) patients had RA, including seropositive disease in 37, seronegative in 15 and juvenile idiopathic arthritis (JIA) in 10 patients (Table 2). Forty-two (40%) patients had SpA with ankylosing spondylitis in 18, psoriatic arthritis in 8, seronegative oligoarthritis in 5, enteropathic arthritis in 4, reactive arthritis in 4 and sacroiliitis in 3 patients (Table 2).

### *Drug survival in infliximab treated RA and SpA patients*

At the two years' time point, forty-one (40%) patients had achieved at least a 50% treatment response and the treatment was still on-going (Table 1). In nine of them, the infliximab treatment was, however, transiently halted during the two years' follow-up due to a specific reason (1 infection, 5 remissions, 1 migraine, 1 loss of efficacy, and 1 adverse event from another drug). During two years of follow-up, the infliximab treatment had been discontinued in 62 patients (60%) (Table 1). One patient moved to

another district and was lost from the follow-up. After two years, 23 (37%) RA patients and 18 (44%) SpA patients were still continuing the infliximab treatment (Table 2). In those patients in this group, the number receiving glucocorticoid treatment had declined from 93% to 78% and the mean equivalent dose of prednisolone from  $10.2 \pm 1.1$  to  $4.7 \pm 0.54$  mg/day (mean  $\pm$  SEM  $p < 0.0001$ ) during two years of infliximab treatment.

The reasons for discontinuation of infliximab treatment during two years of follow-up are shown in Table 3. During two years' follow-up, 14 patients achieved remission lasting at least six months. However, seven out of the 14 patients re-initiated infliximab treatment during the follow-up due to disease activation, and thus seven patients were still in remission without infliximab treatment at the two years' time point.

The treatment was withdrawn from 23 (22%) patients due to poor efficacy. Six patients discontinued the treatment already during the first seven months because an adequate response was not attained. Seventeen patients, who initially exhibited an appropriate response, were forced to discontinue due to reducing efficacy.

In twenty-five (24%) patients, infliximab was discontinued due to an adverse event (Table 4). Nine of the adverse events were infections and 14 were hypersensitivity reactions. Two patients discontinued infliximab treatment due to leukopenia. In five patients, infliximab was discontinued for other reasons, i.e. intention to conceive ( $n=2$ ), technical difficulties in vein cannulation ( $n=2$ ), and maxillary sinus operation ( $n=1$ ). Two patients died during the follow-up, one after cerebral infarction and one after myocardial infarction

### *Infections*

We defined nine patients with infections that compelled discontinuation of the infliximab treatment during two years' follow-up. Most of these infections appeared during the first year, only one after 22 months of infliximab treatment. Five of the nine infections were pneumonias. One pneumonia patient suffered for several months from fluctuating fever and dyspnoea, and she was eventually diagnosed to have mediastinal tuberculosis.

Two cases of septic arthritis appeared during the follow-up, one patient with arthritis in the ankle joint caused by *Staphylococcus aureus* and another with arthritis in the knee caused by *Staphylococcus species*. One patient had a generalized infection with elevated CRP (145 mg/l) with no clinically evident infection focus being detected (Table 4). One 75-year-old female patient suffered from an asymptomatic recurrent urinary tract infection and infliximab treatment was discontinued.

#### *Hypersensitivity reactions*

Fourteen of the 25 adverse events that required the discontinuation of the infliximab treatment were hypersensitivity reactions (Table 4), including acute infusion reactions like urticaria, rash, itching or oedema in eleven patients, and delayed hypersensitivity reactions in three patients. All hypersensitivity reactions were reduced after discontinuation of the infliximab infusions and glucocorticoid treatment. Three patients were not receiving ongoing glucocorticoid treatment at the time of the hypersensitivity reaction.

#### *Other adverse events*

Two patients developed leukopenia related to infliximab, and the treatment was discontinued. In one 58-year-old patient, with neutrophils  $1.4 \times 10^9/l$ , conventional DMARD's (sulphasalazine and methotrexate) were first discontinued without improvement. Discontinuation of infliximab infusions resulted in a favourable response and leukocyte levels became normalized. Another patient experienced recurrent leukopenia (neutrophils  $1.1 \times 10^9/l$ ). Discontinuation of conventional DMARDs had no effect, and leukopenia was only relieved after discontinuation of the infliximab treatment.

## Discussion

The treatment of rheumatic diseases with biologicals in Pirkanmaa Health Care District including city of Tampere (serving a population of about 500.000) is concentrated in the Center for Rheumatic Diseases, Tampere University Hospital. In the present study, all the patients (n=104) treated with infliximab as their first biological treatment for active RA or SpA according to the national guidelines during 1999-2005 in the Center for Rheumatic Diseases, were analyzed. Infliximab treatment was started for patients with active disease according to the discretion of an experienced rheumatologist, not as a randomized enrolment in a clinical trial. Thus this analysis of the patient records analyses data of the outcomes of infliximab treatment in everyday practice in one rheumatological centre.

The main goal in the treatment of active RA can be set to achieve and maintain remission with a combination of anti-rheumatic drugs [20, 21]. According to the national guidelines, infliximab treatment is added to combination DMARD therapy when patients have severe and refractory RA despite active treatment with traditional DMARDs. Contrary to the situation in randomized clinical trials, the patients in the present survey had severe and aggressive disease despite ongoing treatment with combinations of two or more DMARDs, not only MTX which is the case in most randomized clinical trials with TNF $\alpha$  inhibitors. In addition, the doses and numbers of glucocorticoids and NSAIDs were adjusted by the treating rheumatologist.

In the present study, we were able to retrieve patient records during the two years follow-up from all patients who started the treatment with infliximab except for one subject who moved to another district. A significant loss of patients during follow-up is quite a common phenomenon in many, especially observational, studies [22-24]. Concomitant DMARDs, especially methotrexate, when combined with biological treatment enhance compliance to the treatment [25] and this may have influenced the very good adherence to the treatment also in the present survey. Combination therapy with methotrexate and infliximab achieved a better response than methotrexate or infliximab as monotherapy [2-4]. As mentioned previously, combination therapy with two or more DMARDs is widely used in Finland [20, 21] and a biological drug is frequently to supplement combination DMARD therapy. In our previous study, we have shown that in patients with refractory RA or SpA, the addition of etanercept or adalimumab to a combination of traditional DMARDs, resulted in good compliance as well as a favourable treatment response during 12 months' follow-up [26].

In the initial clinical randomized studies, Maini et al reported continuation rates up to 91% with ACR20 criteria after 30 weeks' infliximab treatment depending on the dose and infusion intervals [1], and in the study of Lipsky et al. a continuation rate of 79% was reported after 54 weeks' treatment [2]. In observational studies, continuation rates are usually lower than in clinical randomized trials, 66% of the patients continued infliximab infusions after one year [8] and after two years' intervention 67% [9] and 73% [10] drug survival rates were reported. In the study of Buch et al., only 27 out of 174 patients (16%) continued infliximab treatment at the 24 months' time-point [14]. In the present study, 40% of the patients continued with infliximab treatment after the two years' follow-up

since they had achieved at least a 50% response without any severe adverse event or other reason requiring discontinuation of the treatment. In addition, seven (7%) of 104 patients had discontinued infliximab treatment due to remission.

In the present study, the continuation rate was 35% in RA patients and 44% in SpA patients. Although the difference was small, it confirms the results obtained in previous studies. In a Spanish study, SpA patients had a 33% lower probability to discontinue the biologicals than RA patients [27] and recently also Heiberg et al. reported a higher continuation rate among patients with AS or PsA versus RA patients [28]. In some clinical trials, infliximab has been given at higher doses and/or shorter intervals to patients with SpA than in patients with RA [6, 7]. In the present study, infliximab treatment was started at a dose 3 mg/kg also in SpA patients and if needed, the dose was increased and/or the infusion interval was adjusted in conjunction with the response. Accordingly, Braun and co-workers concluded in their review that often a dose of 3 mg/kg is adequate also in SpA patients [7]. However, there is data showing that increasing the infliximab dose in SpA patients after 36 weeks of treatment from 5 mg/kg to 7,5 mg/kg achieved no better efficacy [6].

The response to infliximab treatment is evident already after two weeks of treatment, when over 50% of the RA patients have been reported to achieve ACR20 response [1]. There is probably some variation in the onset time of the response, and the effect of the drug treatment can also wane with time. It was recently reported that in RA an increase in frequency of infusions may contribute to more a constant effect than an increase in the dose [29]. In the study of Figueiredo et al., nearly 40% of the RA patients required an increase of the dose or a shortening of the interval between the infliximab infusions or

both to maintain relief of symptoms [16]. In the present study, the average discontinuation time among the 23 patients with an inadequate response was 11 months after treatment initiation. According to the patients' records, 6 / 23 patients discontinued the treatment due to inadequate response during the first seven months, and 17 / 23 patients had an appropriate response at the beginning but discontinued the treatment later because of waning efficacy. Buch et al. reported also that some patients could not maintain an already achieved response at later time points [14]. In observational studies, the rate of discontinuation due to inefficacy varies between 9.2-11% [8, 10, 16]. In clinical studies, discontinuation rates due to inefficacy are around 10 % [1, 2]. It is worth noticing the continuation criteria in those studies have been mostly set as ACR20 and not ACR50 as in the present study which is the clinical practice in Finland.

The formation of antibodies against infliximab has been reported in clinical trials [1, 3] and anti-infliximab antibodies are more often found in patients with reduced response [30]. In addition, there is also evidence about the association between antibody formation and increased infliximab clearance [31, 32]. In the present study, antibodies against infliximab were not measured. It is possible that the dissipating efficacy was due to decreased concentrations of active infliximab as a result of the formation of infliximab-antibody-complex or to differences in the metabolism of infliximab in individual patients [33].

In the present study, only those adverse events that led to discontinuation of infliximab treatment were registered. Those were serious and often required either medical treatment or hospitalization. During the two years follow-up, 24% of all patients were compelled to discontinue the medication due to adverse events. Infection were responsible for

discontinuation of the treatment in 9% of the patients. In RA, there is an increased risk for infections [34, 35]. Traditional DMARDs have been reported to further elevate the risk [36-38], but there are also contradictory findings [39]. Biologicals have also a tendency to increase the risk of infections [11, 40, 41] in RA patients. We observed in the present study a higher number of infections which caused discontinuation of treatment during the first year of the treatment than in the second year. These data are in agreement with the results of Curtis et al. who reported a 4-fold greater risk of infections during the first 6 months of infliximab treatment [40]. The most frequently occurring severe infections during infliximab treatment are pulmonary, skin, soft tissue, joint and bone infections, and also septic infections are slightly more probable in RA patients treated with biological agents than in those treated with conventional DMARDs [11-13, 41]. Oral glucocorticoids have also been reported to elevate the risk of infections in patients with RA even at a dose under 5 mg/day [36, 38, 39]. In active and severe RA or SpA, the use of biologicals in addition to combinations of DMARDs and oral glucocorticoids is probably associated with a high risk for infections and this should be taken into account clinically, and when interpreting the results of the present study.

Hypersensitivity reactions appear to be related to infliximab infusions quite often, but these are usually benign. In previous reports, hypersensitivity reactions have been a notable reason for discontinuation of infliximab treatment, and they have most frequently occurred during the second to fourth infusion [14, 15] manifesting as urticaria, rash, itching and dyspnoea. In the clinical study of Maini et al. [1], hypersensitivity reactions appeared most commonly during the first infusion. In our study, 13% of the patients had to discontinue infliximab treatment due to a hypersensitivity reaction and half of these

reactions occurred during the first six months. In the present study, three patients with a hypersensitivity reaction were not receiving glucocorticoid treatment in addition to the infliximab and DMARDs. Augustsson et al. [42] reported that daily low-dose glucocorticoids lowered the risk of treatment-limiting infusion reactions to infliximab.

In previous studies, only a few cases of leukopenias have been reported [9, 43-45]. In the present study, two patients developed leukopenia during the two years of follow-up. In a recent analysis of 1440 patients with rheumatic disease who were treated with a biological drug, four patients with leukopenias were reported [46].

In the present study, RA and SpA patients with active disease despite ongoing treatment with combinations of DMARDs were treated with infliximab as their first biological drug. Drug survival after two years of follow-up was 40%, when ACR50 (or 50% reduction in BASDAI) was set as the response criteria. As compared to our previous results with six months' follow-up [18], drug survival decreased, mainly due to waning efficacy and an increasing number of adverse events. Infections and hypersensitivity reactions were the most common adverse events which were responsible for the discontinuation of treatment. In addition, two patients with drug related leukopenia were diagnosed.

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**Table 1.** Characteristics of the patients treated with infliximab.

	At the beginning		After two years infliximab treatment				
	Started	Continued	Discontinued				
	All (n = 104)	All (n = 41)	All (n = 62)	Remission (n = 7)	Inadequate response (n = 23)	Adverse event (n = 25)	Other reason (n = 7)
Age, years, mean (range)	45 (18-75)	44 (22-74)	48 (22-76)	44 (22-59)	43 (29-62)	51 (23-75)	55 (24-71)
Females (%)	62 %	49 %	71 %	86 %	57 %	76 %	86 %
Disease duration, years, mean (range)	12 (0.8-52)	15 (3-31)	13 (1-53)	12 (1-26)	10 (2-23)	15 (2-53)	15 (3-29)
Number of concomitant DMARDs							
0 (%)	5 %	7 %	13 %	0 %	4 %	20 %	28 %
1 (%)	37 %	37 %	35 %	57 %	35 %	32 %	29 %
2 (%)	29 %	19 %	31 %	29 %	26 %	36 %	29 %
3 or more (%)	29 %	37 %	21 %	14 %	35 %	12 %	14 %
Glucocorticoid intake (%)	91 %	78 %	84 %	71 %	91 %	88 %	100 %
Glucocorticoid dose (mg/day)	10	4,8	7,8	3,9	10,4	9,1	9,5

DMARD, disease modifying antirheumatic drug.

One patient was lost during the follow-up (moved to another district).

**Table 2.** Infliximab treated patients according to the diagnosis.

Diagnosis	At the	Continuing after	
	beginning,	two years,	
	n = 104	n = 41	(40%)
	n	n	%
Rheumatoid arthritis	62	23	37 %
Seropositive rheumatoid arthritis	37	9	24 %
Seronegative rheumatoid arthritis	15	8	53 %
Juvenile idiopathic arthritis	10	6	60 %
Spondyloarthropathies	42	18	44 %
Ankylosing spondylitis	18	8	42 %
Psoriatic arthritis	8	2	25 %
Seronegative oligoarthritis	5	3	60 %
Enteropathic arthritis*	4	2	50 %
Reactive arthritis	4	2	50 %
Sacroiliitis	3	1	33 %

RA, rheumatoid arthritis; SpA, spondyloarthropathy;

\*Arthritis associated with Crohn's disease or ulcerative colitis.

**Table 3.** Reasons to discontinue infliximab treatment.

Reason	Number	%*
Remission	7	11
Lack of efficacy	23	37
Adverse event	25	40
Other reason	7	11
Total	62	100

\* % of patients who discontinued the medication

**Table 4.** Adverse events which led to discontinuation of infliximab treatment.

Classification	Nr	Diagnosis	Age (years)	Sex	Disease duration (years)	DMARD's	Time of adverse event (months)	Adverse event
Infection	1	Seronegative oligoarthritis	43	F	19	PRED 5 mg/day MTX 25 mg/wk HCQ 257 mg/day	11	Septic arthritis of right knee joint
	2	Seropositive rheumatoid arthritis	49	F	6	MTX 10 mg/wk CyA 200 mg/day SSZ 2000 mg/day	1.5	Pulmonary tuberculosis with mediastinum lymph nodes, diagnosed by biopsy
	3	Seronegative rheumatoid arthritis	51	F	7	PRED 10 mg/day MTX 25 mg/wk	5	Infection (CRP 145 mg/ml) with unknown focus
	4	Ankylosing spondylitis	54	M	7	PRED 15 mg/day MTX 25 mg/wk SSZ 2000 mg/day	11	Pneumonia
	5	Ankylosing spondylitis	57	M	15	PRED 7.5 mg/day SSZ 2000 mg/day HCQ 300mg/day	22	Pneumonia
	6	Seropositive rheumatoid arthritis	58	F	26	PRED 15 mg/day ATM 50 mg/6wk HCQ 300mg/day	3	Septic arthritis of right ankle joint
	7	Ankylosing spondylitis	60	M	12	SSZ 2000 mg/day	3	Pneumopericarditis
	8	Seropositive rheumatoid arthritis	71	F	12	PRED 10 mg/day AF 9 mg / day	2	Pneumonia
	9	Seropositive rheumatoid arthritis	75	F	16	PRED 5 mg/day LEF 20 mg/every other day	9	Recurrent urinary tract infections
Hypersensitivity reaction	1	Seropositive rheumatoid arthritis	23	F	2	PRED 5 mg/day	22	Infusion reaction (pain and swelling of throat)
	2	Seronegative rheumatoid arthritis	28	F	15		6	Infusion reaction (rash), DMARDs stopped previously because of mild pharyngitis
	3	Juvenile idiopathic arthritis	31	F	30	PRED 5 mg/day CyA 100 mg/day SSZ 2000 mg/day AF 3 mg/day	3	Infusion reaction (dyspnea, rash and itching)
	4	Enteropathic arthropathy	31	M	6	PRED 7.5 mg/day CyA 300 mg/day SSZ 3000 mg/day	18	Infusion reaction (headache, dyspnea and rash)
	5	Ankylosing spondylitis	35	M	7	MTX 5 mg/wk	13	Infusion reaction (dyspnea, swelling of throat and erythema of face)
	6	Seropositive rheumatoid arthritis	37	F	21	PRED 7.5 mg/day MTX 22.5 mg/wk	23	Delayed infusion reaction (itching and rash), developed four days after infusion
	7	Seronegative rheumatoid arthritis	40	M	2	PRED 5 mg/day MTX 10 mg/wk SSZ 2000 mg/day	3	Infusion reaction (rash in upper-body)
	8	Seronegative rheumatoid arthritis	47	F	15	PRED 15 mg/day MTX 20 mg/wk SSZ 2000 mg/day	15	Infusion reaction (rash and itching)
	9	Seropositive rheumatoid arthritis	50	F	7	PRED 10 mg/day AZA 50 mg/day	20	Delayed infusion reaction (rash, itching and edema of face), developed few days after infusion
	10	Seropositive rheumatoid arthritis	52	F	6	CyA 150 mg/day SSZ 3000 mg/day HCQ 214 mg/day	5	Infusion reaction (dyspnea, rash and cough)
	11	Seropositive rheumatoid arthritis	54	F	11	PRED 10 mg/day MTX 20 mg/wk	1.5	Infusion reaction (sickness, chills and rash)
	12	Seropositive rheumatoid arthritis	73	F	25	MTX 5 mg/wk	15.5	Infusion reaction (rash and itching in the hand)
	13	Psoriatic arthropathy	73	F	15	PRED 10 mg/day	5.5	Delayed infusion reaction (rash, dyspnea), developed two days after infusion
	14	Seropositive rheumatoid arthritis	75	F	53	PRED 5 mg/day CyA 100 mg/day SSZ 2000 mg/day	6	Infusion reaction (hoarseness, dyspnoea, rash)
Other reason	1	Seropositive rheumatoid arthritis	44	F	15	PRED 10 mg/day CyA 150 mg/day HCQ 214 mg/day	24	Recurrent cytopenia/neutropenia (0.85-1.1 x 10 <sup>9</sup> /l)
	2	Enteropathic arthropathy	58	F	22	PRED 5 mg/day SSZ 1000 mg/day	5	Cytopenia/neutropenia (1.4 x 10 <sup>9</sup> /l)

DMARD, disease modifying antirheumatic drug; AF, auranofin; ATM, aurothiomalate; AZA, azathioprine; CyA, cyclosporin A; HCQ, hydroxychloroquine; MTX, methotrexate; PRED, prednisolone; SSZ, sulfasalazine

