British Journal of Medicine & Medical Research
2(1): 39-53, 2012

SCIENCEDOMAIN *international*
www.sciencedomain.org

The Safety and Effectiveness of Single and Repeat Dosing of Intra-Articular Anti-Tumour Necrosis Factor Treatment after Failure of Intra-Articular Steroids

Justin Chia[1] and Janet Pope[2*]

[1]Division of Rheumatology, Department of Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada.
[2]St. Joseph's Health Care, 268 Grosvenor St., London, ON, Canada, N6A 4V2.

Research Article

Received 29th August 2011
Accepted 19th November2011
Online Ready 6th December 2011

ABSTRACT

Objectives: To determine if intra-articular (ia) anti-tumour necrosis factor (TNF) yielded benefit in patients failing ia steroid injections and determine the safety and durability of single and repeated ia anti-TNF treatment in inflammatory arthritis.
Methods: Patients with inflammatory arthritis having one or two active joints, and having failed previous ia steroids were injected with ia adalimumab or ia etanercept mixed with triamcinolone and lidocaine via a retrospective chart audit.
Results: Twenty-six patients were followed: 18 received ia adalimumab, 12 received ia etanercept and 4 received both. Twenty-five knees, 17 ankles, 1 wrist and 1 PIP were injected of whom 6 had repeated injections to a joint. Nine were on concomitant systemic anti-TNF therapy. Fifteen had RA, 4 had a seronegativearthropathy, 3 had psoriatic arthritis, and 4 had other arthritis. When determining a response to ia anti-TNF for $\geq$ 2 months in patients with sufficient follow up 13 of 18 receiving iaadalimumab and 6/7 with ia etanercept had benefit. There were no serious adverse events (SAEs) and only one AE in a wrist post ia adalimumab, with rebound inflammation after 6 weeks of marked relief. Two were able to cancel or postpone joint surgery(knee and ankle)and one cancelled an yttrium injection.
Conclusions: There were no SAEs and prolonged benefit was found with ia anti-TNF and steroids and lidocaine compared to previous ia steroids with lidocaine in the majority (20/27). Although not approved for ia administration, ia anti-TNFs may be cost effective in persistent synovitis of one or two joints recalcitrant to ia steroids.

**Corresponding author: Email: janet.pope@sjhc.london.on.ca;*

Keywords: Inta-articular; injection; anti-tumour necrosis factor; inflammatory arthritis.

1. INTRODUCTION

Tumour necrosis factor-alpha (TNF-α) has been recognized as important in the pathogenesis of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) (Neidel et al., 1995), and has been an effective target for treatment. Anti-TNF-α agents such as adalimumab, etanercept, infliximab, golimumab and certolizumab block TNF-α (Gartlehner et al., 2006). Despite differences in dosing and route of administration, it appears that anti-TNF-α agents do not differ significantly among each other in regards to efficacy (Gartlehner et al., 2006).

Anti-TNFs are costly and have side effects such as increasing common and serious infections, reactivating tuberculosis and causing cytopenias and elevated liver enzymes, and malignancies (Scheinfeld, 2005; Bongartz et al., 2006). Therefore to increase synovial bioavailability and to decrease systemic side effects, it has been proposed that an intra-articular (ia) delivery system could maintain a therapeutic concentration and provide a local sustained drug action over longer time periods (Butoescu et al., 2009). In RA cases with discrete joint flares or resistant monoarthropathiesia drug delivery may also prove more practical and cost-effective than other parenteral drug routes (e.g. IV, sc) (Larsen et al., 2008). Traditionally, the mainstay ia drugs used in inflammatory arthritis have been corticosteroids (CS), but recently there have been studies and case reports implementing ia anti-TNF-α agents. In one case series, 3 patients with ankylosing spondylitis were injected with infliximab into the knee, and after 4 weeks their arthritis had completely subsided (Schatteman et al., 2006). In a study using iaetanercept in RA wrists, elbows, ankles, and finger and toe joints were injected and both tenderness and swelling decreased significantly after 1 week and 1 month. In nine of the cases tested, a reduction in synovial thickness was demonstrated (Bliddal et al., 2006b). In a case report, adalimumab was injected into a knee with reduction in pain and stiffness for 3 months (Kobak, 2008). However, to our knowledge there are no studies using ia adalimumab with larger sample sizes or results past 1 year. To date, there have been few more robust studies using ia anti-TNFs. One randomized controlled trial (RCT) using ia etanercept in RA patients found that after one month there was no significant difference between ia steroids and anti-TNFs in those who had not previously been treated with ia steroids (Bliddal et al., 2006a). A placebo-controlled study was done by Osborn (Osborn, 2002) also using ia etanercept in RA patients and over 4 months of follow-up there was found to be an improvement in joint inflammation as compared to ia saline. Despite many trials using ia anti-TNFs, mostly small case reports, the ability of ia anti-TNFs in treating joints recalcitrant to steroids has not been studied, and patient follow-up has been short. To date, there are no studies with ia adalimumab and repeated injections. Recent TNFi given intra-articularly has been reviewed (see Table 1).

The objective of this pilot study was to determine the efficacy, safety, and length of benefit of ia adalimumab and ia etanercept in patients with inflammatory arthritis with persistent synovitis of one or two joints after failing intra-articular steroids.

2. METHODS

This study was conducted by means of a chart review. Under the guidance of the attending rheumatologist, patients were identified that had received ia adalimumab (40 mg) or ia etanercept (50 mg) (except a smaller dose for a PIP joint). The study was approved by the University of Western Ontario Ethics Committee. In general, patients had been considered for ia anti-TNF-α if they had: 1) experienced symptoms of moderate to active disease in one or two joints, 2) had residual joints despite DMARDs or systemic biologic treatment, and 3) had previously failed at least one ia steroid injection, often obtaining less durability of response with repeated ia steroid injections. Patients were eligible if they had ongoing joint synovitis in one or two joints despite DMARD or systemic biologic treatment, and the joints were recalcitrant to ia steroids. The anti-TNF selected to inject ia was based on availability of supply in the clinic and thus there was no bias in what to use. Some patients were injected with a different anti-TNF than they were on systemically. Initially only adalimumab samples were available but later etanercept was also attained.

Chart reviews were performed on all participants to determine inflammatory arthritis diagnosis, previous and current DMARDs and biologic treatment, adverse events from the ia anti-TNF injections (AEs), total number of past ia steroid and anti-TNF-α injections, joints injected and duration of response (how long the ia anti-TNF worked and if continuing, the length of follow up). We also determined the safety and efficacy of those who received repeated injections and other potential benefits such as removing patients from joint surgery waiting lists.

Injection technique. Eligible patients were warned of the possible side effects of ia anti-TNF-α agents prior to treatment and were informed that ia injection was not an approved method of administration. Using clean technique, 40 mg of adalimumab or 50 mg of etanercept was mixed in a 3 cc syringe with 1 cc of triamcinolone and 1 cc of 1% lidocaine (except in the PIP where no steroids or lidocaine were given in order to ensure enough volume and 0.3 cc of adalimumab was given alone). For the injections, a 25 gauge, 1.5 inch needle was used to inject into the joints. Abbott and Amgen/Wyeth provided the anti-TNF drugs used, which are normally used for patients obtaining coverage for subcutaneous use to bridge patients until coverage was obtained. The pharmaceutical companies had no input into the trial, nor did they approve the use of the samples provided for this purpose. Patients were followed at their next regular appointment and were asked at subsequent visits, and also via a phone interview (approved by the University of Western Ontario Ethics Committee), about side effects, reduction in pain, longevity of effects, and if there were improvements in function. Effectiveness of the ia anti-TNF treatment was based on the patient's opinion and physical examination. Standardization of care was achieved by having the same rheumatologist administering the treatment and following all patients in the study.

3.RESULTS

Twenty-six patients were found to have met the study criteria over a four-year period (2005-2009): 6 males aged 34 to 81 years and 20 females aged 27 to 68 years. Fifteen had RA, 4 had a seronegativearthropathy, 3 had PsA, 1 had systemic onset JIA disease, 2 had connective tissue disease of whom one overlapped with RA, and 1 patient had Crohn's associated arthritis with a positive RF (which therefore may have been RA). Nine were on anti-TNF therapy at the time of the ia anti-TNF injection. Table 2 shows the baseline characteristics of the patients treated.

Table 1. Summary of studies with intra-articular anti-TNF treatment

Source	Type of Study	Disease Treated	Anti-TNF Drug	Duration of Follow-up, months	Outcome	Comment
Dreher et al. (Dreher et al., 2001)	Case series (n=3)	RA	Infliximab	4	+ Infliximab injections superior to previous ia steroid injections	Small case series
Bokarewa and Tarkowski (Bokarewa et al., 2003)	Case series (n=6)	AS, PsA, RA, ReA, JIA	Infliximab	2	- Infliximab no better than local injection of ia steroids.	Small case series, short follow up
Nikas et al. (Nikas et al., 2004)	Pilot study (n=5)	RA	Infliximab	1.5	+ Reduction in swelling, tenderness, pain.	Small cases series, short follow up
Schatteman et al. (Schatteman et al., 2006)	Case series (n=3)	AS	Infliximab	1	+ Decrease in synovial thickening and ia fluid by MRI.	Small cases series, short follow up
Conti et al. (Conti et al., 2008)	Case series (n=17)	RA, PsA	Infliximab	12-26	+ Efficacious even in those receiving systemic TNFα antagonists.	Larger case series with longer follow up
Alstergren et al. (Alstergren et al., 2008)	Case report (n=1)	PsA	Infliximab	8	+ Repeated injections into TMJ reduced persistent pain and improved mobility.	Only one patient
Ahern et al. (Ahern et al., 2008)	Case report (n=1)	Seronegative spondyloarth-ropathy	Infliximab	12	+ Resistant knee monoarthritis now in remission.	Only one patient

Table 1 continues……..

Conti et al. (Conti et al., 2005)	Case report (n=1)	HLA-B27-positive Spondyloarth-ropathy	Infliximab	8	+ Complete remission of knee arthritis.	Only one patient
Bliddal et al. (Bliddal et al., 2006b)	Pilot study using randomized doses of etanercept (n=26)	RA	Etanercept	1	+ No adverse events, all doses showed same results, significant decrease in swelling and tenderness after 1 week 15/24 improved pain at one month	Trying to determine dose, no control, very short follow up
Bliddal et al. (Bliddal et al., 2006a)	RCT (n=38)	RA	Etanercept	0.25	- Similar effects from both ia etanercept and steroids.	RCT, but short follow up (1 week), not the patients in whom you would likely consider ia TNF as patients had not failed (or received) prior ia steroids.
Osborn (Osborn, 2002)	Placebo-controlled study (n=20)	RA	Etanercept	4	+ Benefit as compared to saline.	Small positive RCT
Hobbs (Hobbs, 2005)	Case report (n=1)	Sarcoidosis	Etanercept	9	+ Complete and total relief of pain and stiffness.	Only one patient
Arnold et al. (Arnold et al., 2003)	Case report (n=1)	PsA	Etanercept	2	+/- After two injections experienced resolution of swelling and increased ROM, but also had an acute injection site reaction.	Only one patient

Table 1 continues……..

Kobak (Kobak, 2009)	Case report (n=1)	Pigmented villonodularsy novitis	Adalimumab	6	+ Decreased pain on movement, increased joint ROM.	Only one patient
Kobak (Kobak, 2008)	Case report (n=1)	RA	Adalimumab	3	+ Decreased effusion, ESR, CRP, regained ROM.	Only one patient
Bello (Bello et al., 2010)	Case series (n=5)	PsA	Infliximab	0.25 to 6	+ Effective in 4/5, two had repeat injection (one of whom it was effective)	Small n, open label
Haroon (Haroon et al., 2010)	Case report (n=5)	Monoarthritis	TNFi + methylpredni solone	2 to 3 repeated every 2 to 3 months	+/- Effective in 3/5 for a long period of time (median follow up 12 months)	Small n, open label
Cui (Cui et al., 2010)	Case series (n=16)	SI joint in AS	Etanercept	25mg at 0,4,8 weeks 2 months	+ All 16 improved at 8 weeks, BASDAI at 8 and 12 weeks	Unblinded, but all improved
Fiocco (Fiocco et al., 2006)	Case report (n=2)	Pigmented villonodularsy novitis	Etanercept	12.5 mg ia X 4 weeks, then synovectormy	? Synovectomy performed after	Can't tell results as patients had a synovectomy

Table 2. Characteristics of the patients who received intra-articular anti-TNF treatment

Patient Gender	Age	Diagnosis	Disease Duration (Years)	Joint(s) Injected with anti-TNF	Past Number of Triamcinolone Injections to the Joint	Total Number of Adalimumab Injections	Total Number of Etanercept Injections	Past DMARDs	Current DMARDs
M	46	Seronegative arthritis	11	Left knee	12	1	---	HCQ	HCQ
F	68	RA	15	Left knee	2	1	---	D-pen, HCQ, Gold, Leflunomide, Mtx, MI, SSZ	---
F	35	RA/CTD	4	Left knee in suprapatellar bursa	2	1	---	Etanercept, HCQ, Mtx, Rituximab	HCQ, Rituximab
				Right ankle	1	1			
F	36	RA	8	Left ankle	4	1	---	Adalimumab, CQ, Etanercept, HCQ, Mtx, SSZ	Adalimumab, HCQ, Mtx
F	43	Seronegative arthritis	5	Left knee	1	1	---	SSZ	SSZ
F	60	RA	2	Left knee	7	2	---	HCQ, Mtx, SSZ	HCQ, Mtx, SSZ
F	59	RA	>15	Right ankle	4	2	---	Adalimumab, Goldold, HCQ, Leflunomide, Mtx, SSZ	Adalimumab, Leflunomide
M	64	Seronegative arthritis	8	Left ankle	3	1	---	MI, SSZ	SSZ
M	34	Systemic onset JIA	29	Right knee	16	1	---	Etanercept, Infliximab, Mtx, Anakinra, Prednisone	Mtx, Anakinra
F	45	RA	10	Right knee	6	2	---	Etanercept, HCQ, Infliximab, Leflunomide, Mtx, SSZ, Rituximab	Leflunomide, Rituximab
M	38	RA	10	Left knee	15	4	---	Adalimumab, HCQ, Mtx, SSZ	Mtx
F	47	RA	1	Right ankle	2	1	---	Leflunomide, Mtx, SSZ	Leflunomide, Mtx, SSZ
F	62	RA	14	Right ankle	3	1	1	Adalimumab, HCQ, Mtx, SSZ	Adalimumab, HCQ, Mtx, SSZ
M	58	RA	39	Right ankle	13	4	1	Etanercept, HCQ, Mtx, SSZ	Etanercept, Mtx
F	46	RA	12	Right wrist	4	1	---	HCQ, Leflunomide, Mtx, SSZ	HCQ, Leflunomide

Table 2 continues……..

F	64	Psoriatic arthritis	32	Right knee	6	---	1	HCQ, Mtx, SSZ	HCQ, Mtx, SSZ
F	66	Seronegative arthritis	19	Left Knee, Right knee	6	---	2	HCQ, Mtx, SSZ	HCQ, Mtx
F	37	Psoriatic arthritis	19	Left knee	1	1	1	CQ, Leflunomide, Mtx, SSZ	SSZ
F	42	Crohn's and +RF	8	PIP finger		1	--	Mtx, Adalimumab, Prednisone, SSZ	Mtx, Adalimumab, Prednisone
F	62	Psoriatic arthritis	18	Right knee Left Knee	6	--	1 1	Mtx, SSZ, Gold, Etanercept	Etanercept
F	66	CTD	10	Right knee Left knee	8 8	--	1 1	Mtx. HCQ, SSZ, Leflunomide	Mtx, Leflunomide
F	27	RA	5	Left ankle	1	--	1	Mtx, Etanercept, HCQ	Mtx, Etanercept
F	50	RA	4	Left Knee	4	--	1	Mtx, HCQ, SSZ, Prednisone, Adalimumab, Etanercept	Mtx, Etanercept, Prednisone
F	46	RA	17	Left knee Right knee	2 2	--	1 1	Mtx, HCQ, SSZ, Leflunomide, Gold, MI	SSZ, Gold
F	31	RA	10	Right ankle Left ankle	3 3	1	1	Mtx, Prednisone, Infliximab, Etanercept	Mtx, Etanercept
M	81	RA	13	Right ankle	5	--	1	Mtx, Anakinra, HCQ, Prednisone, SSZ, Leflunomide	Mtx, Etanercept

CQ = Chloroquine; D-pen = D-pencillamine; E = Etanercept; HCQ = Hydroxychloroquine; Gold = Myochrysine; Mtx = Methotrexate; MI = Minocycline; SSZ = Sulfasalazine

Table 3. Outcomes from the intra-articular anti-TNF injection

Patient Gender	Age	Anti-TNF Injected	Benefit from Intra-articular Injection	Duration of Benefit	Adverse Events	Duration of Follow-up (Months)
M	46	Adalimumab	+	3 months	-	10
F	68	Adalimumab	-	Few days	-	5
F	35	Adalimumab	+ ankle - knee (suprapatellar bursa)	>6 months for ankle Knee only relief for days	-	6 and still improved
F	36	Adalimumab	+	>5 months	-	7
F	43	Adalimumab	+	4 months	-	9
F	60	Adalimumab	+	3 months	-	16
F	59	Adalimumab	+	3 months (first) 6 months (second)	-	19
M	64	Adalimumab	-	Few days	-	50
M	34	Adalimumab	-	Few days	-	8
F	45	Adalimumab	+	3 months	-	19
M	38	Adalimumab	+	4 months	-	55
F	47	Adalimumab	+	2 months	-	5
F	62	Adalimumab/Etanercept	+	4 months	-	10
M	58	Adalimumab 4 times Etanercept once	+	$\geq$4 months	- Prior to last ia anti-TNF treatment, we had none available and tried again ia steroids alone which did not work at all	36
F	46	Adalimumab	+	6 weeks	Rebound inflammation of wrist following two weeks of dramatic pain relief.	3
F	64	Etanercept	+	2 weeks	-	2
F	66	Etanercept	+	4 months (Right) 2 months (Left)	-	4

Table 3 continues……..

F	37	Etanercept Adalimumab	+ insufficient FU for adalimumab injection	>5months	-	5 0.5
F	42	Adalimumab	+	>2 months	-	2
F	67	Etanercept	+	Ongoing >1 month	-	1
F	66	Etanercept	+ -	Ongoing >7months Left knee only worked for 3 weeks	-	7
F	27	Etanercept	+	Ongoing>1 month	-	1.5
F	50	Etanercept	+	Ongoing>1 month	-	2
F	46	Etanercept	+	Ongoing >4 months Ongoing >1 month	-	4
F	31	Etanercept Adaliumab	+	Ongoing >1 month	-	1
M	81	Etanercept	+	Ongoing >3 months	-	3.5

+ = Prolonged benefit; - = No benefit; ? = Follow-up too short to determine

Over the 4 years of the study, 18 patients received ia adalimumab (total 28 injections), 12 patients received ia etanercept (total 16 injections), and 4 received both; 25 knees, 17 ankles, 1 wrist and 1 PIP were injected of whom 6 had repeated injections to a joint and some had two joints done at one visit (Table 2). Thus, there were a total of 44 ia anti-TNF joint injections.

When determining a response of ia anti-TNF for $\geq$ 2 months13 of 18 patients who received ia adalimumab injections, and 6/7 with ia etanercept, had benefit (as at the time of writing this manuscript 5 who received etanercept did not have long enough follow up to rate the treatment as a sustained success but had improvement > 1month). Symptom relief described included decreased pain, stiffness, and swelling. A few patients reported dramatic improvement. One RA patient had inadequately responded to both sc etanercept and sc adalimumab, in addition to methotrexate, leflunomide, and sulfasalazine. She subsequently had a good response to iv rituximab while on background leflunomide except for a persistent right knee effusion that had been injected 6 times with steroids and drained several times prior to steroid injections. She had ia adalimumab into her right knee with excellent results and was able to cancel her scheduled total knee replacement (TKR) and 1.5 years later she still has not needed a TKR. Another patient (male with RA) receiving chronic sc etanercept and methotrexate had several ia adalimumab injections to his ankles which allowed him to postpone ankle surgery for three years.His other joints were in remission. There has been no evidence of attenuation of ia adalimumab effects over three years. Another patient with persistent synovitis of her knees, despite other joints doing well with sulfasalazine and injectable myochrysine and having synovitis recur after yttrium injections (within months), was able to cancel a repeat yttrium after anti-TNF injections and discontinue gold therapy.

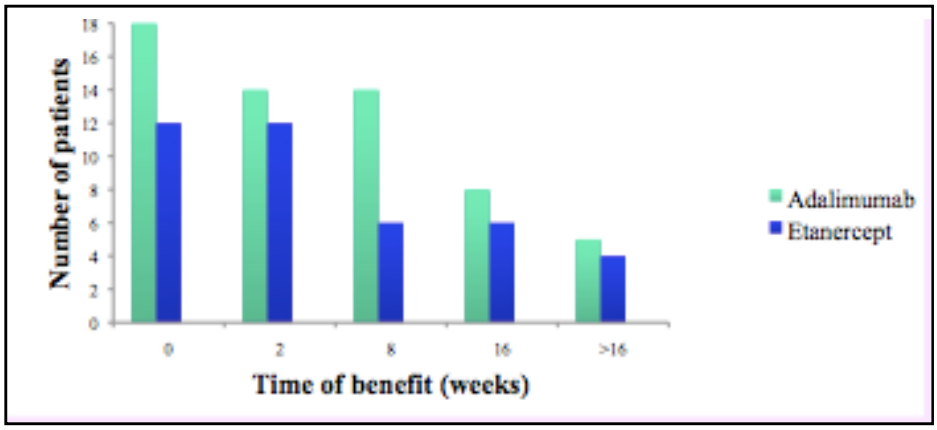

Figure 1. Early Results at Single site for iaTNFi injections with Adalimumab and Etanercept

72% of patients after ia adalimumab and 86% of patients after ia etanercept had benefit for at least 8 weeks. Follow up is limited so this is a conservative estimate as some patients were not yet followed beyond 8 weeks. Some patients may have had longer benefit but the data are truncated at last follow up or phone call.

A patient with seronegative oligoarthritis who had previously failed twelve ia steroid injections (which only were successful for a couple of weeks over the previous few years) and yttrium prior to ia adalimumab did not respond to ia anti-TNF treatment. He re-accumulates effusions of 40 to 120 cc.He is an athlete and has maintained joint space so he

has been referred for a surgical synovectomy. Many patients who were treated with oral prednisone to control their oligoarticular joint flares after they ceased to have an ia steroid response no longer required themafter receiving ia anti-TNF treatment.

Duration of symptom relief ranged from 2 weeks to >6 months in those that received benefit, and only a few days in the four patients that did not. Every patient received some relief and all joints were concomitantly injected with ia steroids (despite previous failure) except the one PIP joint. A few patients reported overall joint improvement, so they likely had some systemic absorption, but the non-injected joint improvement only lasted for a few days. For those with success, all stated the ia anti-TNF was lasting longer or worked better than their previous ia steroid injection.

Six patients received repeat injections into the same joint with continued benefit. One patient reported an AE after ia adalimumab into the wrist. She experienced symptom relief for six weeks with marked improvement after failing repeated ia steroid injections (stating her wrist felt the best it had in years), but after 6 weeks had rebound inflammation not correlated with an infection requiring oral prednisone to treat the wrist. There were no other AEs (Table 3. Duration of follow-up ranged from 3 to 50 months (Table 3). Figure 1 shows the response to treatment with ia TNFis.

4. DISCUSSION

To our knowledge, this is the first study using ia adalimumab in a larger sample size, with longer follow up and repeated injections. As other intra-articular studies have demonstrated (Bliddal et al., 2006b; Bliddal et al., 2006a; Osborn, 2002), our results seem to indicate that ia adalimumab is a safe use of the drug which works well to alleviate residual joints following treatment with DMARDs. The results we report with etanercept are different than past trials, which compared ia etanercept with ia steroids in the short term and did not study ia steroid failure patients (Bliddal et al., 2006b; Bliddal et al., 2006a).

Only one patient experienced an adverse rebound reaction.It could be expected that using ia anti-TNF-α agents would result in an increased incidence of serious infections as a systemic dose is localized into a single joint (Schiff et al., 2006). However, there would be less systemic exposure if a patient who was not on background anti-TNF treatment received occasional ia injections and this could potentially decrease the risk of infections. Our present study unfortunately lacks the sample size to determine the absolute safety of ia administration, but data indicate that dissolved small-molecule drugs are rapidly cleared from the synovial space after ia injection, with steroids having a $t_{1/2}$ of only1.3 hours but the effect can last longer (Larsen et al., 2008). Findings of systemic improvements have been seen in other studies using ia infliximab in patients with active RA suggesting that the drugs do leave the synovium (Dreher et al., 2001). The benefits seen from ia administration may be attributed to an increased bioavailability into the synovial space, as sc administration may only result in synovial concentrations being 31% of the serum levels (Schentrup, 2003). Further studies could make use of an injectable depot formulation in which the biologic is released in a controlled manner, thereby prolonging local effects and providing greater control of the drug (Butoescu et al., 2009; Larsen et al., 2008).

Overall, duration of efficacy was similar to past studies using ia biologics with benefit ranging from a few weeks to several months (Kobak, 2008; Conti et al., 2005). One must interpret findings with a degree of caution, as patients could have recall bias, and our study was not blinded or randomized. To limit recall bias, many were interviewed shortly after the ia

injection and then followed routinely over time. Patients served as their own controls by comparing previous ia steroid injections against both ia steroids and anti-TNF-α combined. Due to the retrospective nature of the study, HAQ and pain scores were not recorded at regular monthly intervals after the injections were done. In the future, a more controlled prospective study may resolve many of these limitations. It may be that there is an advantage to combining ia anti-TNF with ia steroids in previous steroid non-responders. Many of our patients had initially responded well to ia steroids and then the response diminished over time.

Table 1 reviews many studies using ia anti-TNFs in the treatment of various rheumatological diseases. Our study is concordant with their findings in that there were little to no AEs using single or multiple injections of ia anti-TNFs and the injections were efficacious in the treatment of monoarthropathies recalcitrant to steroids. Only one AE has been recorded in past studies, which was a local reaction to a second ia etanercept injection into the knee thought to be a reaction or a low grade infection that resolved with time and antibiotics (Arnold et al., 2003; Bliddal, 2004). In the study by Osborn *et al* (2002) using ia etanercept, tenderness and swelling decreased in the injected joints and effects were seen for several months, which is similar to some of our patients. Our study demonstrates potential benefit of repeated ia TNF inhibitor injections. Intra-articular targeted therapies to reduce TNF expression, such as using a TNF antagonist gene in a viral vector,are a further possibility (Mease et al., 2010).

Patients did not chase their background drugs unless they did not have an ongoing response at one month. An ia steroid injection was considered a failure for this study when it did not work for at least one month by patient history and an active joint was present that had previously been injected with intra-articular steroids. An active joint had to be both swollen and tender with signs of significant inflammation (heat).

The choice of TNFi between adalimumaband etanercept was actually made by availability in the clinic fridge. Initially, we thought adalimumab was preferred due to a longer dosing half-life than etanercept, but began using etanercept as we had 'samples' available. If both were available we used whichever the patient was receiving systemically (if they were on a biologic) or we arbitrarily chose one. The dose was decided to be a full injection dose except for the PIP where volume was limited to 0.3 cc. The dose was arbitrary: 50 mg of etanercept or 40 mg of adalimumab, which may not be equivalent due to the frequency of dosing (adalimumab is dosed in inflammatory arthritis half as frequently as etanercept). However, there was some literature to guide the dosing (from previous reports). The procedure seems safe and many patients gain symptomatic relief, at least in the short-to-medium term. The generalizability is high as these are varied inflammatory arthritis patients, often with failure of multiple steroid injections where ia TNFis have been tried.

Overall, this study seems to indicate that ia anti-TNF-α agents are safe and often effective in treating residual joints that are resistant to ia steroids. In patients with one or two remaining joints despite background therapy and failing intra-articular steroids, ia anti-TNFs with steroids and lidocaine may be a cost effective alternative to treating with systemic biologics. Indeed, we had two patients that had damaged and active joints who were able to postpone joint surgery. The comparative benefits of this approach to performing an yttrium synovectomy are unknown. The majority of patients having been treated with ia-anti-TNFs have had a sustained positive benefit and repeated injections have demonstrated sustained response.

The success rate appeared similar between adalimumab and etanercept despite the potentially longer half-life of adalimumab, which may have been due to the large concentration in the joint with each product. Benefit for at least two months in 76% seemed high despite several patients failing multiple ia steroid injections, and thus this form of treatment seems feasible in the recalcitrant patient who has only one or two active joints. There may or may not be added benefit combining ia anti-TNF with ia steroids and certainly there were not safety issues with this technique.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

REFERENCES

Ahern, M.J., Campbell, D.G., Weedon, H., Papangelis, V., Smith, M.D. (2008). Effect of intra-articular infliximab on synovial membrane pathology in a patient with a seronegative spondyloarthropathy. Ann Rheum Dis., 67, 1339-42.

Alstergren, P., Larsson, P.T., Kopp, S.(2008). Successful treatment with multiple intra-articular injections of infliximab in a patient with psoriatic arthritis. Scand J Rheumatol., 37, 155-7.

Arnold, E.L., Khanna, D., Paulus, H., Goodman, M.P. (2003). Acute injection site reaction to intraarticular etanercept administration. Arthritis Rheum., 48, 2078-9.

Bello, S., Bonali, C., Serafino, L., Di, Giuseppe, P., Minosi, A., Terlizzi, N. (2010). Intra-articular therapy with infliximab in psoriatic arthritis, efficacy and safety in refractory monoarthritis, (Italian). Rheumatismo. Jan-Mar., 62(1), 46-50.

Bliddal, H. (2004). Intraarticular injection of anti-tumor necrosis factor, Comment on the letter by Arnold et al. Arthritis Rheum., 50, 2037-8.

Bliddal, H., Terslev, L., Qvistgaard, E., et al. (2006a). A randomized, controlled study of a single intra-articular injection of etaercept or glucocorticosteroids in patients with rheumatoid arthritis. Scand J Rheumatol., 35, 341-5.

Bliddal, H., Terslev, L., Qvistgaard, E., et al. (2006b. Safety of intra-articular injection of etanercept in small-joint arthritis: an uncontrolled, pilot-study with independent imaging assessment. Joint Bone Spine, 73, 714-7.

Bokarewa, M., Tarkowski, A. (2003). Local infusion of infliximab for the treatment of acute joint inflammation. Ann Rheum Dis., 62, 783-4.

Bongartz, T., Sutton, A.J., Sweeting, M.J., Buchan, I., Matteson, E.L., Montori, V. (2006). Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies, systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA, 295, 2275-85.

Butoescu, N., Jordan, O., Doelker, E. (2009). Intra-articular drug delivery systems for the treatment of rheumatic diseases, a review of the factors influencing their performance. Eur J Pharm Biopharm., 73, 205-18.

Conti, F., Priori, R., Chimenti, M.S., et al. (2005). Successful treatment with intraarticular infliximab for resistant knee monarthritis in a patient with spondylarthropathy, a role for scintigraphy with 99mTc-infliximab. Arthritis Rheum., 52, 1224-6.

Conti, F., Ceccarelli, F., Priori, R., Iagnocco, A., Signore, A., Valesini, G. (2008). Intra-articular infliximab in patients with rheumatoid arthritis and psoriatic arthritis with monoarthritis resistant to local glucocorticoids. Clinical efficacy extended to patients on systemic anti-tumour necrosis factor alpha. Ann Rheum Dis., 67, 1787-90.

Cui, Y., Xiao, Z., Shuxia, W., Zhenjun, Z., Hengguo, Z., Liangyi, F., et al. (2010). Computed tomography guided intra-articular injection of etanercept in the sacroiliac joint is an effective mode of treatment of ankylosing spondylitis. Scand J Rheumatol. May, 39(3), 229-32.

Dreher, R.F.W., Leitzeke, D. (2001). Treatment of rheumatoid arthritis by intra-articular injections with TNFa blockers [abstract]. Arthritis Rheum., 44.

Fiocco, U., Sfriso, P., Oliviero, F., Sovran, F., Scagliori, E., Pagnin, E., et al. (2006). Intra-articular treatment with the TNF-alpha antagonist, etanercept, in severe diffuse pigmented villonodularsynovitis of the knee. (Italian) Reumatismo. Oct-Dec., 58(4), 268-74.

Gartlehner, G., Hansen, R.A., Jonas, B.L., Thieda, P., Lohr, K.N. (2006). The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol., 33, 2398-408.

Haroon, M., O'Gradaigh, D. (2010). Efficacy and safety of combining intra-articular methylprednisolone and anti-TNF agent to achieve prolonged remission in patients with recurrent inflammatory monoarthritis. Joint Bone Spine. May, 77(3), 232-4.

Hobbs, K. (2005). Chronic sarcoid arthritis treated with intraarticular etanercept. Arthritis Rheum., 52, 987-8.

Kobak, S. (2008). Monoarticular rheumatoid arthritis treated with intra-articular adalimumab. Mod Rheumatol., 18, 290-2.

Kobak, S. (2009). Intraarticularadalimumab in a patient with pigmented villonodularsynovitis. Rheumatol Int.

Larsen, C., Ostergaard, J., Larsen, S.W., et al. (2008). Intra-articular depot formulation principles: role in the management of postoperative pain and arthritic disorders. J Pharm Sci., 97, 4622-54.

Mease, P.J., Wei, N., Fudman, E.J., Kivitz, A.J., Schechtman, J., Trapp, R.G., Hobbs, K.F., et al. (2010). Safety, tolerability, and clinical outcomes after intraarticular injection of a recombinant adeno-associated vector containing a tumor necrosis factor antagonist gene: results of a phase 1/2 Study. J Rheumatol. Apr., 37(4), 692-703.

Neidel, J., Schulze, M., Lindschau, J. (1995). Association between degree of bone-erosion and synovial fluid-levels of tumor necrosis factor alpha in the knee-joints of patients with rheumatoid arthritis. Inflamm Res., 44, 217-21.

Nikas, S.N., Temekonidis, T.I., Zikou, A.K., Argyropoulou, M.I., Efremidis, S., Drosos, A.A. (2004). Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: a pilot study. Ann Rheum Dis., 63, 102-3.

Osborn, T. (2002). Intraarticular etanercept versus saline in rheumatoid arthritis, a single injection double-blind placebo controlled study [abstract]. Arthritis Rheum., 46.

Schatteman, L., Gyselbrecht, L., De, Clercq, L., Mielants, H. (2006). Treatment of refractory inflammatorymonoarthritis in ankylosing spondylitis by intraarticular injection of infliximab. J Rheumatol., 33, 82-5.

Scheinfeld, N. (2005). Adalimumab, a review of side effects. Expert Opin Drug Saf., 4, 637-41.

Schentrup, A. (2003), Adalimumab (Humira) novel human monoclonal antibody for the treatment of rheumatoid arthritis. PharmaNote., 18, 1-8.

Schiff, M.H., Burmester, G.R., Kent, J.D., et al. (2006). Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis., 65, 889-94.