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ORIGINAL ARTICLE

A feasibility study for a randomised controlled trial of treatment withdrawal in psoriatic arthritis (REmoval of treatment for patients in REmission in psoriatic ArThritis (RETREAT (F))

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Abstract TNF therapy is effective for all aspects of psoriatic disease, but these drugs are costly and the long-term effects are unknown. Further, methotrexate causes concern with long-term adverse events. The purpose of this pilot study was to test the feasibility of drug withdrawal from patients with psoriatic arthritis, in stable low disease state. We examined the availability of patients, their willingness to participate, study procedures, and the proportion of patients in the withdrawal arm who relapsed during the study. Low disease state was defined by minimal disease activity criteria (MDA), and relapse by failure to achieve these criteria. Patients in the withdrawal group underwent a phased withdrawal of medication where the last treatment added was the first withdrawn. Assessments were monthly for 3 months before study exit. Seventy-two patients were invited to participate, of which 57 were found to be eligible. Twenty-six (36.1 %) subsequently attended the screening visit but 9 failed eligibility criteria so that 17 patients (29.8 % of the 57 eligible patients, 95 % confidence interval (CI) 18.4, 43.4 %) were randomised at a ratio of 2:1 in favour of the withdrawal arm (11 withdrawals, 6 standard care). Six patients experienced a flare, all of whom were in the withdrawal arm (relapse rate 54.6 %, 95 % CI 23.4, 83.3 %). Four of the flares were apparent from visit 3 (8 weeks after starting withdrawal). Given the high relapse rate, an alternative trial design of partial treatment withdrawal, possibly including a patient preference arm, is recommended.

Keywords Adverse events · Disease activity · Psoriatic arthritis · Treatment withdrawal

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Introduction

Psoriatic arthritis is defined as an inflammatory arthritis affecting the joints and connective tissue and is associated with psoriasis of the skin or nails [1]. The prevalence of psoriasis in the general population in Northern Europe has been estimated to be between 2 and 3 %, and the prevalence of inflammatory arthritis in patients with psoriasis has been found to be up to 30 % in secondary care populations and probably half that in the community [2, 3].

There is little evidence for most traditional disease-modifying anti-rheumatic drug (DMARD) treatments in psoriatic arthritis, but tumour necrosis factor (TNF) therapy, also known as biologic therapy, is effective for all aspects of the disease, including extra-articular features [4, 5].The long-term effects of biologic therapy are unknown. Studies of the economic impact of RA in the UK before the introduction of biologic therapies found that direct health care costs represented about one quarter of all costs, and these were dominated by inpatient and community day care [6], with DMARD drugs representing a minor proportion: 3–4 % of total costs and 13–15 % of direct costs. Evidence from the USA suggests that expenditure on biologics might represent 35 % of direct cost

[7], but similar data are not yet available for the UK [8]. Increasing expenditure on biologics might be at least partly offset by cost savings elsewhere [9], though as yet the evidence for this is only suggestive. If patients experienced some degree of treatment interruption whilst remaining in remission, this would significantly reduce the treatment cost for PsA patients in the UK.

For these reasons, evidence to support a reduction or withdrawal of therapy in psoriatic arthritis is required. It has recently been shown that remission may be sustained despite treatment interruption [10], but two further trials, published since the inception of the current study, have suggested that complete withdrawal of treatment leads to relapse in the majority of patients [11, 12].

The purpose of the current study was to test the feasibility of a randomised controlled trial of treatment withdrawal in patients with psoriatic arthritis in stable low disease activity in an ambulatory setting of UK rheumatology practice. We examined such items as the availability of patients in a low disease state, their willingness to participate, study procedures and the proportion of patients in the withdrawal arm who relapsed during the observation phase of the study.

Methods

Full ethical and MHRA approval was obtained. Patients were recruited from outpatient clinics in the UK. The inclusion criteria were (1) age ≥18 years, (2) diagnosis of peripheral psoriatic arthritis of more than 12-month duration (according to CASPAR Criteria [13]), (3) in minimal disease activity (as defined by the MDA criteria [14]), (4) stable disease for the preceding 6 months as indicated by the treating physician and (5) on a stable dose of TNF or DMARD for the 6-month period directly preceding screening.

Participants attended an initial screening visit (visit 0) where consent was obtained; a clinical assessment was undertaken; and MDA was confirmed utilising the MDA criteria. At baseline (visit 1), a full assessment was undertaken. Those who remained in MDA were randomised at a ratio of 2:1 in favour of the withdrawal arm using a secure remote computer service. Following randomisation, patients were assessed at monthly intervals until the final visit (visit 4) when their participation in the study terminated. Patients were given a telephone number to call and could be reviewed between scheduled visits if necessary.

Clinical assessment consisted of patient-reported outcomes (PROMs) and physical examination. PROMS included visual analogue scales, SF36 [15], and health assessment questionnaire (HAQ [16]). Physical examination and disease assessment included tender and swollen joint counts, dactylitis assessment, enthesitis assessment, psoriasis area severity assessment (PASI [17]), body surface area of psoriasis (BSA), modified nail psoriasis severity index (mNAPSI [18]) and physician VAS of overall disease activity. The assessments permitted the calculation of a composite disease activity score, the psoriatic arthritis disease activity score (PASDAS [19]), in addition to an assessment of MDA. A complete assessment was performed at baseline (visit 1) and week 12 (visit 4): at other visits, only data sufficient to calculate the MDA score were collected. Safety blood tests (FBC, LFT, and U&E) and efficacy blood tests (CRP, PV and ESR) were collected at every visit.

Patients in the withdrawal group underwent a phased withdrawal of medication (for their psoriatic arthritis) where the last treatment added was the first withdrawn (Table 1). Treatment was withdrawn in a stepwise fashion phasing out and stopping over 4 to 8 weeks.

The definition of flare was based on the MDA criteria: not being in MDA at any of the visits after baseline was considered to be a flare of disease. If there was evidence of disease flare, medication was re-introduced, with use of intra-muscular, oral or intra-articular steroids if required.

Adverse events (AEs), including serious adverse events (SAEs), were collected for all patients from randomisation until the last dose of treatment with a protocol IMP. AEs and SAEs were evaluated for duration and intensity according to the NCRI Common Toxicity Criteria. In this study, since medication was withdrawn, no further data were collected after the end of the trial schedule (16 weeks after randomisation).

Statistical methods

Formal sample size calculations were not performed for this pilot study. A sample size of 30 patients (randomised 2:1 withdrawal arm vs control) was deemed sufficient to achieve the study aims.

No formal statistical comparisons were planned between study groups as this was a small pilot study. Descriptive statistics were used to report each outcome measure. The observed relapse rates were reported with 80 % exact confidence intervals to inform sample size calculations for a future study.

Table 1 Schedule for drug withdrawal

Summary of treatment withdrawal	
Etanercept injections	Weeks 0, 2, 4 and 8
Adalimumab injections	Weeks 0, 4 and 8
Infliximab infusion	Weeks 8 or 10
Golimumab injections	Week 6
MTX	Step-wise reduction of 2.5 mg per week until cessation
All others	Dose halved for 6 weeks and then stopped

MTX methotrexate

Table 2 Baseline disease characteristics

Mean (SD); median (range)	Randomisation arm		Overall
	Standard care (n=6)	Withdrawal (n=11)	
Years since onset of skin symptoms	9.6 (7.7); 6.1 (2 to 21)	19.2 (14.6); 16.8 (4 to 49)	15.6 (13.0); 12.3 (2 to 49)
Years since onset of joint symptoms	5.3 (3.0); 4.7 (2 to 11)	7.1 (6.3); 5.3 (2 to 19)	6.4 (5.3); 4.9 (2 to 19)
Years since psoriasis diagnosis	9.0 (8.3); 5.6 (1 to 21)	16.6 (14.8); 16.4 (2 to 49)	13.5 (12.9); 7.3 (1 to 49)
Years since PsA diagnosis	3.7 (1.9); 3.7 (1 to 7)	6.1 (6.1); 3.5 (1 to 17)	5.3 (5.1); 3.5 (1 to 17)
CASPAR criteria (n (%) PSA)	5 (83.3 %)	9 (81.8 %)	14 (82.4 %)
Body surface area percentage	0.5 (0.6); 0.5 (0.0 to 1.0)	0.7 (2.1); 0.0 (0.0 to 7.0)	0.7 (1.8); 0.0 (0.0 to 7.0)
PASI score (0–72)	0.4 (0.5); 0.4 (0.0 to 1.2)	0.3 (0.5); 0.0 (0.0 to 1.6)	0.4 (0.5); 0.0 (0.0 to 1.6)
Dactylitis score (0–20)	(0.0); 0.0 (0.0 to 0.0)	0.2 (0.6); 0.0 (0.0 to 2.0)	0.1 (0.5); 0.0 (0.0 to 2.0)
mNAPSI score (0–520)	1.8 (3.0); 0.0 (0.0 to 7.0)	1.3 (2.4); 0.0 (0.0 to 6.0)	1.5 (2.5); 0.0 (0.0 to 7.0)
Physicians global VAS (0–100)	2.8 (1.8); 4.0 (0.0 to 4.0)	5.5 (5.0); 4.0 (0.0 to 17.0)	4.6 (4.4); 4.0 (0.0 to 17.0)

Results

Seventy-two patients were invited to participate in the study, of which 57 were found to be eligible. Twenty-six (36.1 %) subsequently attended the screening visit during the recruitment period allocated. Nine patients were found not to be in the required minimal disease activity (MDA) state either at screening or the subsequent baseline visit. Therefore, a total of 17 patients (29.8 % of the 57 eligible patients, 95 % confidence interval (CI) 18.4, 43.4 %) were randomised. Six patients were randomised to standard care and 11 to treatment withdrawal. All patients were followed up to the planned 4-month time point. There were no withdrawals or patients lost to follow-up (Fig. 1).

There were more males than females in the study (six treatment withdrawals, four standard care). The mean age of the

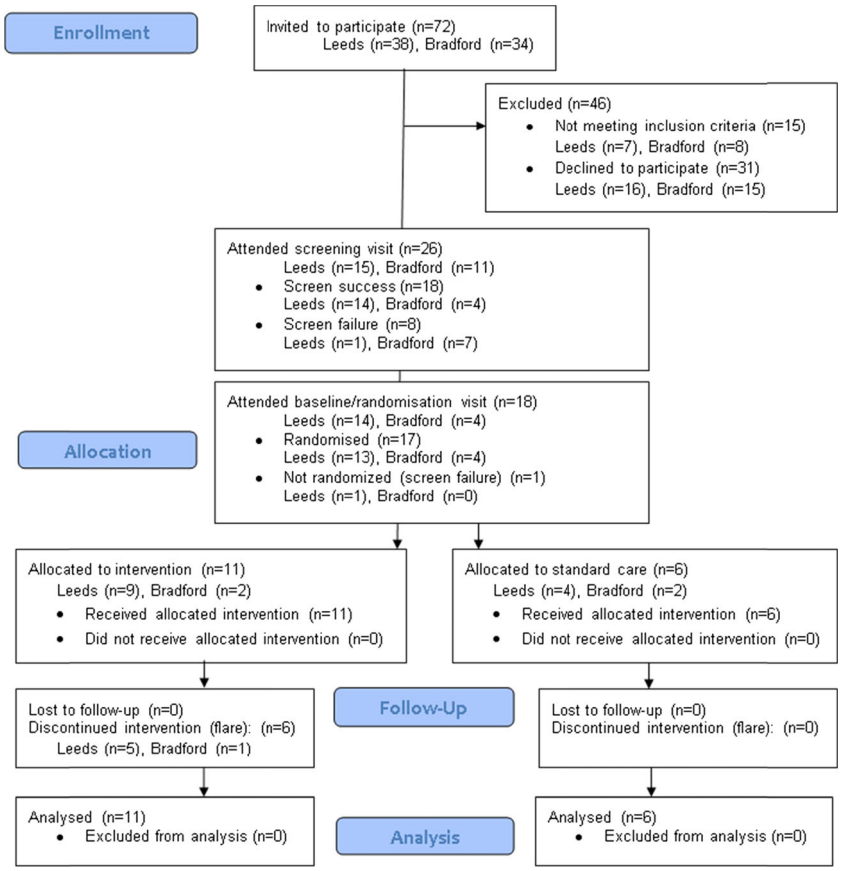

Fig. 1 CONSORT diagram for study

Table 3 Medications at screening

Medications at screening	Randomisation arm				Overall	
	Standard care		Withdrawal			
	N	%	*N*	%	*N*	%
MTX only	5	83.3	3	27.3	8	47.1
MTX+other DMARD	0	0	2	18.2	2	11.8
MTX+biologic	1	16.7	5	45.5	6	35.3
Biologic only	0	0	1	9.1	1	5.9

patients was 52 years. Table 2 summarises the main disease characteristics for the randomised patients at screening. The majority of the standard care arm (5/6, 83 %) were on methotrexate (MTX) alone on entry into the study (Table 3). Forty-five percent of the withdrawal arm was on MTX plus biologics and 27 % on MTX alone.

Six patients experienced a flare, all of whom were in the withdrawal arm (relapse rate 54.6 %, 95 % CI 23.4, 83.3 %). In the majority of cases (n=4), the flares were apparent from visit 3 (8 weeks after starting withdrawal). Of the six patients who flared, four were on MTX and a biologic (flaring on withdrawal of the biologic) and two were on MTX only. Cases are summarised by treatment arm in Table 4.

Mean PASDAS at screening for cases was 1.40 and at visit 4, 2.23. Amongst cases who experienced a flare, these figures were 1.14 and 2.78, respectively. The same figures for the control arm were 1.36 and 1.33. Cut-offs for disease activity for PASDAS have been developed [20].The cut-off for low disease activity is <3.20. It should be noted that only three cases were in a 'flare' as defined by this cut-off at the final visit.

There were no serious adverse events. There were eight adverse events from seven of the study patients (two standard care patients and five withdrawal arm patients). All adverse events were deemed to be mild severity and not related to the study treatments.

The Trial Steering Committee recommended follow-up of all cases in the withdrawal arm 3 months after the end of the trial. Two of the three patients in a flare at the end of the study were still in a flare although each case was improving with further treatment modification.

The relapse rate in the standard care arm was zero, but our study only contained six patients on standard care. The relapse rate in the withdrawal arm in this study was 54.6 %, i.e. 45 % of the withdrawal arm was relapse-free. An 80 % confidence interval around this estimate from 16.8 to 76.6 % was calculated to aid sample size estimation for a full study of withdrawal.

Table 4 Flare summary: flare by visit (0=no, 1=yes) with PASDAS and CRP

Id	Visit 0		Visit 1		Visit 2		Visit 3		Visit 4			Overall flare status
	PASDAS	CRP	Flare	CRP	Flare	CRP	Flare	CRP	Flare	CRP	PASDAS	
Cases												
100	0.55	<5	0	<5	0	<5	1	6.0	0	<5	2.37	1
101	1.27	<5	0	<5	0	<5	1	<5	0	<5	1.23	1
102	0.72	<5	0	20.0	0	<5	0	<5	0	<5	1.42	0
104	1.89	<5	0	<5	0	<5	1	<5	1	<5	2.95	1
106	1.58	<5	0	<5	0	<5	0	<5	0	<5	0.75	0
107	0.87	<5	0	<5	1	<5	1	<5	1	<5	3.52	1
109	0.84	<5	0	<5	0	<5	0	<5	1	60.0	3.84	1
110	2.95	<5	0	83.0	0	<5	0	<5	0	<5	1.84	0
111	1.94	<5	0	<5	0	<5	0	<5	0	20.0	2.70	0
201	1.39	<5	0	<5	0	<5	0	<5	0	<5	1.67	0
202	1.40	<5	0	<5	0	<5	1	<5	0	<5	n/a	1
Total			0		1		5		3			6
Controls												
103	1.16	<5	0	<5	0	<5	0	<5	0	<5	1.34	0
105	n/a	9.0	0	7.0	0	n/d	0	5.0	0	8.0	1.17	0
108	1.50	17.0	0	25.0	0	24.0	0	16.0	0	30.0	0.70	0
112	1.74	20.0	0	<5	0	<5	0	<5	0	<5	2.38	0
200	1.04	<5	0	<5	0	5.0	0	6.0	0	<5	1.01	0
203	n/a	<5	0	<5	0	<5	0	<5	0	<5	1.35	0

n/a not available

Table 5 Summary of recent studies of treatment withdrawal in psoriatic arthritis

Study	Cases	Biologics (%)	Flare (%)
UK (current)	11	6 (55 %)	6 (64 %)[a]
Chimenti et al. [12]	47	47 (100 %)	47 (100 %)[b]
Araujo et al. [11]	26	11 (42 %)	20 (77 %)

[a] Four further cases flared after the study ended

[b] Patients were observed up to the point of relapse

Conclusions

This pilot study has provided useful information on drug withdrawal in psoriatic arthritis. Firstly, the planned sample size of 30 patients in 6 months of recruitment from two centres was not achieved. Secondly, the relapse rate was higher than expected and occurred in patients on both MTX and biologics. For these reasons, a larger study using this trial design is unlikely to achieve its objectives or be acceptable to patients.

Recruitment was more difficult than expected, partly due to patients taking action to either stop or reduce the dose of their medication prior to formal enrolment and without discussion with their treating rheumatologist (this occurred following a number of focus groups on treatment withdrawal as part of the preliminary work required for the study). No systematic data are available on the patients who voluntarily reduced their drugs but tapering of treatment does seem possible as many remained 'well' after this reduction. This applied both to treatment with MTX monotherapy and patients taking biologic drugs, who achieved a reduction by extending the interval between doses.

In addition, fewer patients than expected fulfilled the entry criterion of being in MDA, either at screening or at baseline. This reinforces the need to undertake objective assessments of disease activity at each clinic visit. Simply asking patients how they are feeling is insufficient to detect who is in, by definition, minimal disease activity. We acknowledge that patients may be satisfied with their disease activity at states higher than those defined as MDA. However, people with psoriatic arthritis in MDA are close to the patient acceptable state [21] and disease activity higher than this might be expected to be unacceptable to most patients.

We also found a higher than predicted relapse rate in patients in the withdrawal arm. At the time the study was designed, evidence suggested that up to 50 % of people in remission could successfully stop their medication [10]. However, since the initial publication there have been two other studies in which a high relapse rate was observed [11, 12] (Table 5). The current study found a similar relapse rate to the latter studies. Anecdotally, we observed a further four patients in the withdrawal arm experiencing a flare soon after the study was completed and one of the standard care patients had a post-study flare following drug withdrawal. Fortunately, in the current study and in the other withdrawal studies, patients regained low disease activity after restarting their former disease modifying treatment.

In conclusion, given the high relapse rate at 3 months, a fully powered 12-month trial of withdrawal would be unethical. An alternative trial design of partial treatment withdrawal, possibly including a patient preference arm might be preferable, but further studies are required.

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Disclosures None.

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