Dose reduction of biologic therapy in inflammatory arthritis: a qualitative study of patients' perceptions and needs

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Abstract (245 words)

Objective: Successful biologics Disease Modifying Anti-Rheumatic Drug (bDMARD) dose reduction appears increasingly possible from clinical trials. This study aimed to understand the patient perspective of bDMARD dose reduction.

Methods: Patients with RA, AS or PsA who were self-administering subcutaneous bDMARDs therapy at two NHS Trusts participated in semi-structured interviews. To capture multiple experiences, patients were purposefully sampled for a range of age, gender, disease duration, reducing/not reducing bDMARDs and either within 3-12 months of bDMARD initiation or ≥12 months and in remission/low disease activity. Inductive thematic analysis was utilized.

Results: 15 patients were interviewed (6 on dose reduction). Five overarching themes were identified. When thinking about dose reduction, patients reflected on their difficult life before bDMARDs ('Where I was then') compared to their transformative effects ('Where I am now'). All raised concerns that dose reduction would take them back to where they used to be ('Fears for the future') and most believed it a cost-cutting exercise. Most had 'Hopes for the future', that reduction would lower their risk of side-effects, and release funds for other patients. They wanted a clear rationale for reduction, collaborative decision-making, and control over flexible dosing ('Information needs').

Conclusion: Patients are fearful of reducing their bDMARDs' dose, having previously experienced uncontrollable symptoms. However, most were willing to try, provided there was a clear rationale, it was in their best interests, with opportunities for collaboration and dose control. These patient perspectives will inform the provision of patient information to guide clinical discussions.

Keywords: Biologics, bDMARDs, dose reduction, patient perspective, rheumatoid arthritis, ankylosing spondylitis, qualitative

Introduction

Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis (RA, PsA, AS) cause joint pain, stiffness, fatigue and joint damage leading to disability (Suurmeijer et al, 2001). Alongside therapy from multi-disciplinary teams, Disease Modifying Anti-Rheumatic Drugs (DMARDs) aim to reduce inflammatory disease activity. Biologic therapies (bDMARDs) (especially anti- tumour necrosis factor, anti-TNF), which target the drivers of inflammation have proved of great value in inflammatory arthritis over the last 15 years (Nam et al, 2010). For many patients resistant to previous medications, there have been dramatic improvements or even remission. In the UK, the National Institute for Clinical Excellence (NICE) guidelines determine how and when bDMARDs should be started (NICE 2010a; 2010b; 2016a; 2016b): intolerance/inefficacy of DMARDs, plus sustained inflammatory activity (eg Disease Activity Score) (van der Heijde, van't Hof, van Riel, & van de Putte, 1993).

However, long term safety of biologic therapies including local reactions, increased risk of infection and potential malignancy remains unknown () (Holroyd et al, 2018). Furthermore, these agents are expensive compared to conventional synthetic DMARDS (csDMARDs) (circa £9,000/year vs oral methotrexate £40/year). Therefore, to avoid unnecessary patient risk and NHS costs, dose reduction is being investigated. There is increasing RCT evidence that once stable, some inflammatory arthritis patients can reduce the dose of bDMARDs without significant increase in disease activity or reduction in quality of life (van Herwaarden, den Broeder, Jacobs, Bijlsma, Van Vollenhoven, & Van den Bemt, 2014; Fong et al, 2016; Závada et al, 2016; Henaux et al, 2018; Navarro-Compán et al, 2016). However, some patients experience disease flares, requiring re-escalation of bDMARDs. (Edwards, Fautrel, Schulze-Koops, Huizinga, Kruger et al, 2017). Most of the dose reduction data arise from RCTs where patients have been randomized to pre-determined dose reduction regimens (Ibrahim et al, 2017). Little is known about dose reduction in clinical practice, where the reduction regimen could be individually tailored by dose and length of time over which reductions take place.

In clinical practice, patients and clinicians must reach collaborative decisions if patients are to attempt and adhere to dose reduction. In a bDMARD dose reduction trial, 32-56% of patients declined to participate (Marsman et al, 2015). Whilst some declined because it was research, others declined due to anxiety about dose reduction. If bDMARD dose reduction is to be introduced successfully as routine clinical practice it is therefore necessary to understand patients' perceptions and concerns about reduction, in order to guide clinic

discussions and support informed decision-making. The aim of this study was to obtain a greater understanding of the patient perspective of bDMARD dose reduction.

Methods

Research ethics committee approval was obtained (West of Scotland Research Ethics Service, 17/WS/0014) and patients provided written, informed consent. Patients with confirmed RA, AS or PsA who were self-administering subcutaneous bDMARD therapy at two NHS Trusts were invited to participate in semi-structured interviews. They were either approached by a research nurse during a clinic visit, or were mailed an invitation using a departmental database. In one Trust, rheumatologists were collaborating with stable patients to reduce their biologics by increasing the interval between doses using a flexible and individualized approach (Biologics Treatment Reduction by Interval Management, B-TRIM). To capture a broad range of experiences, patients were purposefully sampled to reflect a range of characteristics that might potentially influence their views (Ritchie & Lewis, 2003). Purposeful sampling was facilitated by maintaining a spreadsheet detailing age, gender, diagnosis, disease duration and currently reducing/not reducing biologics for each patient as they were recruited, so that toward the end of recruitment we could 'purposefully' select patients to address any under-represented characteristics. To include perspectives of patients at different stages of treatment, patients were recruited either near the start of therapy (3-12 months) or $\geq$12 months and in stable remission/low disease activity for $\geq$6 months (DAS28 <3.2 in RA; <3 tender and <3 swollen joints in PsA; BASDAI <4 in AS) (Garrett, Jenkinson, Kennedy, Whitelock, Gaisford, & Calin, 1994). It was intended to recruit 15-20 patients, by which point most major themes are likely to have been captured (data saturation) (Guest, Bunce, & Johnson, 2006).

Prior to interview, participants completed a perceived disease activity visual analogue score (VAS 0-10, Not active/very active), Health Assessment Questionnaire for disability (Fries, Spitz, Kraines, & Holman, 1980) and Rheumatoid Arthritis Impact of Disease (RAID) Scale for quality of life (Gossec et al, 2011). The RAID comprises 7 numerical rating scales covering perceived physical symptoms, emotional impact and coping with RA, with a weighted algorithm giving a total score of 0-10 where 10 is worse outcome. One-to-one interviews were conducted (AH-F) in local hospitals or at home, using an interview schedule of neutral, open-ended questions (Table 1) devised by the study team, including patient partners (SF, DN). AH-F first clarified with each patient that dose reduction was a research question, not a personal treatment proposal. Interviews were recorded, transcribed verbatim, anonymized and systematically analysed using inductive thematic analysis (Braun & Clarke, 2006). AH-F and SHew read and re-read all transcripts and important units of meaning were

systematically extracted, grouped into natural sub-themes and then overarching themes, which AH-F explored for links. A subset was independently analysed by team members Sha and SF, followed by a full team discussion of combined findings. Based on these discussions the final themes and sub-themes were refined (SHew). Analysis was iterative, moving back and forth between transcripts, and concurrent with data collection, so that emerging themes could be explored in later interviews. No new major themes arose by interview 15, suggesting data saturation was reached (Guest, Bunce, & Johnson, 2006).

(Insert Table 1 here)

Results

Thirty-eight patients were invited to take part, 18 expressed interest and 15 attended for interview, with interviews lasting approximately 30-60 minutes. Patients included 10 female patients, ranged from 31-77 years, with 5-40 years disease duration (Table 2).

(Insert Table 2 here)

Analysis led to the formulation of five overarching themes (Fig 1):

Theme 1: Where I was then
Theme 2: Where I am now
Theme 3: Fears for the future
Theme 4: Hope for the future
Theme 5: Information needs

These five themes encapsulated 14 sub-themes. The question of bDMARD dose reduction engendered reflection on life both before and after bDMARDs ('Where I was then'; 'Where I am now'), with patients raising both concerns about reduction ('Fears for the future') and potential benefits ('Hopes for the future'), highlighting questions they would like addressed ('Information needs').

(Insert Fig 1 here)

Theme 1: Where I was then

When bDMARD dose reduction was discussed, patients reflected on their life beforehand.

Disease and Life out of control*:* Uncontrolled disease activity before biologics was recalled as overwhelming, with all-consuming pain, loss of function, depression and a sense that life was out of control:

"A 'cocoon of pain' because that's all that's around you. It's everywhere. You can't escape it" (Alison)

"One night with my husband in bed and I couldn't bear the weight of the duvet and I said I just wanted to die. I didn't want to wake up in the morning and I said if I just died tonight I would be happy" (Sally)

"I couldn't sleep, it was affecting my work and I was fatigued, it was affecting my family life and everything" (Alex)

Long journey to biologics: Many felt the process of accessing bDMARDs was long, feeling they had to 'qualify' in order to receive them.

"It was quite difficult to actually get onto the drug. There is a lot of form filling to go through and I think over the years I've taken, I mean to fulfil the criteria, I think it's shown that I'd taken anti-inflammatories, sulfasalazine for a long time" (Deborah)

"You actually had to qualify through a scoring matrix, it was not open for everyone" (Lloyd)

Theme 2: Where I am now

All patients described the transformation that bDMARDs had on their life.

Disease and life under control: bDMARDs had significantly reduced disease activity and pain, improving function, quality of life and enabling return to a more normal lifestyle:

"Less pain or no pain and the fact that I don't get flare-ups" (Kath)

"I couldn't do this and I couldn't do that before, but now I can do anything" (Carl)

"That is when I had the big breakthrough and things started to really improve, and the quality of my life improved enormously" (Lynne)

"It allows me to carry on living my life normally. Yeah, earn money. (laughs) Do you know what I mean? I have to go to work. It allows me to go to work" (Dave).

Miracle drug: For many patients these improvements were dramatic and life-changing.

"It has been a bit of a miracle drug for me really" (Sally)

"I have to admit that was a miracle drug for me and the turnaround was rapid" (Laura)

"It's really transformed my life basically" (Barry)

Theme 3: Fears for the future

Patients feared negative effects of reducing their bDMARDs.

Back to where I was: All patients feared they would return to their previous severe symptoms and poor quality of life, and risk future disease progression:

"I'm scared every time I actually go to see my rheumatologist or the specialist nurse at (hospital) because I just fear that she is going to look at those things and be like 'You are fine now, your inflammation is down so we'll reduce it or we will take you off of it completely'" (Sally)

"Immediate reaction? Fear. Fear of living back with that amount of pain again" (Alison)

"Obviously doing all my fitness things that I am doing, I couldn't have done that before so having the thought that I would get that pain back, get the fatigue back, feel depressed again that would worry me" (Jane)

"It's the pain that I worry about and the development of the disease I guess. Progression of the disease, that's what I don't want, I don't want it to get worse" (Kath)

Some patients felt reliant on the medication, fearing that reducing it might lead to it being withdrawn altogether:

"The longer you have it the more reluctant you are to change your drug" (Meryl)

"I'll tell you what I was concerned about, if I didn't need it every week they might stop me taking the drug, they might turn round and say you don't need it" (Dave)

It's all down to cost: Some patients felt that as bDMARDs are working, there is no reason to stop them, many suspicious that dose reduction was primarily to save money, which might backfire on them and the NHS:

"Why do I need to reduce my amount when the amount that I am taking at the moment works perfectly fine?" (Sally)

"First question, why? (…) So, what could they turn round and say 'Oh we are doing it to save money on the NHS'" (Meryl)

"That's just shifted the cost there, but also you've still got the other medical costs of increasing your pain meds again because that for me would go back up" (Alison)

"No because then you could be going into not being able to work and then you are draining more money from the government in those aspects" (Sally)

Theme 4: Hope for the future

Despite their concerns, all patients hoped lower doses of bDMARDs would have benefits and were willing to try reduction, with the exception of two:

"It just fills me with horror" (Lynne)

"I do realise it is a lot of money to have people taking it (…) I would probably be willing to give them half the amount of money if they paid the other half" (Sally)

Avoid unwanted biologic effects: All patients hoped that dose reduction would lessen potential toxicity:

"I didn't want like, a foreign body being put into me" (Sally)

"Well it's quite worrying sometimes when you think that this is inside you suppressing things which really it's not just suppressing the bad things it may be suppressing good things as well. (…) You sort of think 'My god what's that doing to me?'" (Deborah)

"The risks of taking the drug in the first instance are quite high and they do increase your risks of certain cancers, bowel complaints and all sorts of things, so I think if you can reduce that risk and still get some benefit then why wouldn't you?" (Laura)

Disease controlled, so reduce: Laura (see above), Dave and Carl felt it logical to reduce bDMARDs as their disease was under control; and had initiated widening injection intervals themselves:

"I took it every 2 weeks but now I've started doing it every 3 weeks. (…) Because I am feeling better I started to space it out" (Carl)

"I told myself that I was better and I didn't need it. I thought 'I've had no pain for you know 12 months whatever, so I told myself I was fine, so I stopped taking it" (Dave)

***Hope disease stays controlled*:** Patients hoped that they could reduce their dose and still keep their disease controlled:

"If you can manage on the lesser amount that's how it should be, shouldn't it, which is better for your body and the cost and everything else" (Sharon)

"If you get the same amount of relief but you only take one injection, well that's a bonus" (Alison)

Reducing is more convenient: Some found the routines of bDMARD therapy restrictive or intrusive on their lifestyle:

"I don't like injecting myself. It hurts and it's a bit cold. I hate that" (Dave)

"Sometimes it (biologic therapy) will constrain what you are doing" (Alex)

"We are thinking of going (long haul), aren't we, and that really frightens me because it's such a long travelling time. I wouldn't quite know how to go about taking my biologics with me" (Brenda)

"I also don't like thinking "I'll have to go to (doctor) and get my prescription". You have to wait, I have to have a phone call from (supplier) to say when they are going to deliver. I have to stay in" (Kath)

Dose reduction has allowed more freedom:

"If I have to go to London on a Monday, I think oh my injection wait until Thursday." (Dave)

Save money: Patients knew bDMARDs are expensive and altruistically hoped reduction would lessen NHS costs:

"You are saving lots of money then by not having to keep giving me doses that's not required" (Lloyd)

"That would be great for the NHS and it could be used in better ways like cancer cures and things like that" (Sally)

"Obviously less expensive for the NHS. They can devote their money for other things" (Brenda)

Theme 5: Information needs

Patients had common ideas on information they would need to make a decision about dose reduction.

Making a decision: Patients wanted to understand the rationale behind dose reduction:

"If I went in there and I was told by (nurse) or (rheumatologist) 'Oh we are going to reduce it', I'd say 'Why?' and unless they can give me a valid reason to why, then I would say 'But why me?'" (Meryl)

"If (rheumatologist) was to say 'Actually we want to try and get you off this completely because we think your condition has sort of plateaued'" (Lloyd)

"If the doctors were saying it is affecting you in the wrong way I would then say 'Fine just try it'" (Deborah)

Patients wanted to know whose decision it would be, hoping for a partnership approach:

"I mean the rheumatologists know their patients don't they and it would be kind of partly their decision and partly the patient's I would imagine" (Brenda)

"Being part of a more collaborative kind of process, yeah that would be absolutely fine" (Alison)

Many patients were willing to try reduction as a personal experiment:

"I would be more than happy to extend it and push it as far as I can go and then bring it back if required" (Lloyd)

"I would like to have a month or something off and see what happens. I'd like to try it out, you know" (Kath)

***Practicalities*:** Patients wanted dose reduction to be flexible and individualized, with reassurance they could increase their dose if necessary, with control over dose changes:

"There is no real formula for it I don't think, it is going to be down to the individual" (Barry)

"Reassurance that I could go back to my original dose if I needed it" (Lynne)

"I think I would be in control and if things got bad I know that I would be in control enough to come back onto it and say actually that's not working and I think that they would support me with that decision" (Laura)

"I'm old enough to sort of know my own body, my own pain, so really I should be able to (alter doses)" (Deborah)

Patients wanted information on what symptoms they might experience, reassurance that they could re-escalate bDMARDs, that they would work again, and there would not be the same official lengthy process to re-start:

"What to expect and what might happen in the beginning. Maybe you might experience different pain levels. Would that be normal or not? That kind of scenario really" (Brenda)

"Can you reverse it back to the frequency dose to remove any stiffness that I may get? (…) My only reserve at the minute - whether it can be quickly reversed to go back to that if possible" (Lloyd)

"The fear is that if I was to reduce the dosage and found that problems started to arise, that I wouldn't get the dosage back up again without having to go through the trauma of getting onto it again" (Barry)

Patients wanted support with dose reduction by access to the rheumatology team, and help with scheduling the changing injection dates:

"You've got a rheumatology nurse you feel like you've got a lot of support around you" (Deborah)

"Maybe to produce an app for your phone (…) I think when I was injecting every fortnight it was easier because I did it on a Monday (…) Now because it's not the same day every time that's confused me" (Sharon)

"Yeah, it's just months (calendar) and you circle the day that you injected. (…) I suppose there could be a little space maybe on the back of the form if you've had a particularly bad week, somewhere where you could make a record or a diary of what prompted you to inject earlier" (Laura)

How I want the information:

Patients wanted straightforward information that included the experiences of other patients who have reduced doses, and to talk to other patients:

"In a more sort of layman's language to understand because looking at that (drug leaflet) it's very good but it's very technical" (Brenda)

"Might be useful if there is case history of other people being on it and then being able to gradually reduce it to the point where they don't need it any more" (Barry)

"If I could speak to somebody, true honest experience and ask them the questions because obviously the rheumatologist is probably only going to tell me what I want to hear not what I need to hear" (Sally)

"I think a group session would be probably more useful. Yeah especially when you know they are in the same boat as you would probably sort of get more out of that" (Alison)

Patients said that the potential for future dose reduction could helpfully be mentioned at bDMARD initiation:

"Well I just thought I'd be on the same thing forever really" (Deborah)

"They could tell you about it from the start I suppose. I suppose they could make it more of an option couldn't they? They could say look, this is what we recommend but if you feel confident go for a bit less" (Dave)

Discussion

This study highlights that patients have significant concerns that bDMARD dose reduction would risk losing their current disease control, many assuming it to be a cost-saving exercise. In contrast, they often simultaneously held positive views regarding fewer side-effects, fewer restrictions and better use of NHS resources. Most weighed these in the balance during the interview and in so doing, highlighted the issues they would like addressed during clinic discussions to better inform their decision-making. Crucially, they would like to understand the rationale for dose reduction for them personally. They would like to hear other patients' experiences either included in a dose reduction leaflet, or as a face-to-face group education session.

Whilst most patients hoped for a reduction in side-effect risk and were quite willing (hypothetically) to try dose reduction, two of the 15 patients were not prepared to even consider reduction should it be offered as they felt reduction was to save the NHS money and not in their personal interests. In contrast, three patients had initiated dose reduction themselves, before informing their rheumatology team. A limitation of this study is that no patients were interviewed who had been offered dose reduction clinically and declined it, or tried and failed, which might have broadened the findings. Whilst a strength of this study is that a subset of transcripts were analysed by a patient partner (SF), a limitation is that nobody external to the research team examined any transcripts.

In the early days of bDMARD therapy the possibility of remission and subsequent reduction or discontinuation of therapy were not envisaged and patients in two early qualitative studies expressed great fear that their bDMARD might one day be discontinued and lose the transformation they had brought about (Sanderson, Calnan, Morris, Richards, & Hewlett, 2009; Marshall, Wilson, Lapworth, & Kay, 2004). In this study patients had similar concerns, and also that should bDMARDs need to be re-escalated, they might not be as effective. Furthermore, patients worried they might have to 'qualify' again, repeating the previous long journey for access. Therefore patients' suggestions that the possibility of future dose reduction should be included in information leaflets at bDMARD initiation, is helpful.

Interestingly, many patients cited losing the restrictions of bDMARDs as a possible positive effect of dose reduction, particularly the need to make arrangements to stay in for drug

deliveries and for managing drugs when abroad. It is possible that the transformative effects of bDMARDs mean that they are now working and taking holidays abroad, thus generating previously unforeseen drawbacks to the medication.

These data suggest that clear information on the rationale for biologic dose reduction is needed, and an opportunity for patients to discuss their positive and negative thoughts with the clinician. A leaflet has therefore been produced with the help of the patients on the study team, and is being piloted as the basis for clinic discussions. Patients would like to understand other patients' dose reduction experiences, and it is possible that a decision-aid might help them weigh up what is important to them (Stacey et al, 2017). A clear rationale, open discussion, collaborative decisions, support from and easy access to the team, the ability to decide on their own reduction programme and flexibility to increase bDMARDs again, along with a sense of control, appear to be key factors in decision-making.

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Table 1 Interview guide

For all patients:
What biologic therapy you are on at the moment and how did you get to this point?
If you think your anti-TNF is working, what do you base your judgement on?
What are/were your immediate reactions to the idea of dose reduction?
Why do you think rheumatologists might suggest some people reduce their dose?
Thinking about dose reduction, are there any positive reasons, fears or concerns?
What do/did you think the outcome of dose reduction might be?
What information could/did your clinician provide to help you make a decision on dose reduction?
Would/do you feel confident in being able to monitor your own progress and change your medications to suit how you feel?
Additional questions for patients who had tried to reduce biologics:
Was there any information that would have been useful that you did not receive?
What information would you give to other patients thinking of reducing their dose?
Did you feel involved and in control of the decision making process?
What do you think of the patient record form for dose reduction?

Table 2 Individual participant demographic data

Patient	Gender	Age (yrs)	Diagnosis	Disease duration (yrs)	HAQ†	RAID‡	Disease Activity§	Dose reduction
Lynne	F	68	RA	10	1.125	2.15	1.3	
Lloyd	M	51	PsA	30	0.875	4.81	5.0	Yes
Alex	M	49	PsA	25	2.125	6.35	3.0	
Barry	M	63	AS	40	0.5	0	1.4	Yes
Sally	F	36	PsA	15	0.875	1.63	0.8	
Deborah	F	59	RA	30	1.0	3.0	2.6	
Alison	F	46	AS	5	1.5	3.86	3.4	
Laura	F	40	AS	9	0	0.52	1.4	Yes (self)
Jane	F	31	RA	5	0	0	0.5	
Sharon	F	55	AS	20	1.625	5.87	6.8	Yes
Meryl	F	59	RA	19	2.5	7.30	10.0	
Dave	M	36	AS	9	0.125	2.0	0.6	Yes (self)
Kath	F	70	RA	28	0.75	0.79	0.4	
Carl	M	66	RA	11	1.375	1.38	0.9	Yes (self)
Brenda	F	77	RA	13	1.375	1.38	5.0	

†Health Assessment Questionnaire 0-3 (3 severe disability)

‡Rheumatoid Arthritis Impact of Disease 0-10 (10 severe impact)

§Disease Activity visual analogue scale 0-10 (10 very active)

Fig 1. Conceptual diagram of patient perspectives on biologics dose reduction