ORIGINAL ARTICLE

Qualitative assessment of medication adherence in patients with rheumatic diseases on biologic therapy

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Abstract

Introduction/objectives Despite close management in specialized clinics, medication adherence remains a significant problem for some patients. The study aims to explore factors affecting medication adherence in patients attending a biologics clinic.
Method Participants completed surveys including the Compliance Questionnaire Rheumatology (CQR) to quantify adherence rates. Purposive sampling targeting poorly adherent patients was used to select individuals for qualitative evaluation. Semi-structured interviews were performed and continued until saturation was achieved. Interviews were transcribed and coded using NVivo. Principles of grounded theory were used for data analysis.
Results A total of 123 patients completed the survey (72 RA, 33 PsA, 18 AS). Of which, 96 patients completed all CQR items, of these 72% were identified as adequately adherent. A major theme which emerged from patient interviews was that the presence of active symptoms significantly influenced adherence. Patients tended not to prioritize medication taking until they had a recurrence of symptoms. Despite describing biologics as "life-changing", patients expressed concern regarding potential long-term side effects of these medications which affected adherence. Patients identified their relationship with their rheumatologist as pivotal and perceived diet, exercise and stress as critical. Intentional factors were the predominant drivers for non-adherence; patients made a risk-benefit analysis based on their beliefs and chose to not take their medications as prescribed.
Conclusions Medication adherence to traditional and biological therapies was lower than expected by treating clinicians in this patient group, who are closely supported in a dedicated biologics clinic. Several of the identified themes suggest that shared decision making and enhancing patient education may improve adherence in this group.

Key Points
• *Adherence rates are suboptimal even in supported, educated, English-speaking patients in the biologics era.*
• *Contributing factors were 'intentional' as patients chose to be non-adherent based on their beliefs.*
• *Emergent themes suggest that enhancing patient education could improve adherence.*

Keywords Adherence/compliance · Ankylosing spondylitis · Biologics · Psoriatic arthritis · Qualitative · Rheumatoid arthritis

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Introduction

Poor compliance with the use of prescribed medication is a significant problem. Consequences of non-adherence include poorer patient outcomes; increased disease activity, more disease flares and increased disability [1–3]; and increased healthcare costs, including increased need for inpatient and outpatient medical care and potential escalation of therapy [4–6]. Interventions to improve adherence rates are postulated to have as significant an effect on health outcomes as further developments in traditional biomedical management [7]. High rates of non-adherence to prescribed medications in rheumatic diseases have been reported, with adherence as low as 30% in some studies [4, 5, 8]. Escalation of therapy in the current era

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is particularly of concern, as non-adherence may lead to escalation from conventional therapy to biologic disease-modifying anti-rheumatic drugs (DMARDS), which may pose a significantly increased risk of adverse effects and result in substantial health economic implications.

Measuring patient compliance is important because estimates by experts are shown to be inaccurate. Treating physicians commonly overestimate their patient's adherence, with studies demonstrating their ability to predict non-adherence reported as low as 24% [9, 10]. However, measuring adherence is challenging and may vary widely depending in part on the nature of the study design [4, 11–13].

There are many reasons reported for poor medication adherence [4, 5, 12]. These include concerns by patients regarding the side effects of medications, patients' knowledge of their medical problems, social support and financial issues, use and beliefs regarding alternative therapies, and their relationships with health care providers [4, 5, 8, 14].

Compliance with biologic agents may differ significantly from other medications for a number of reasons including their toxicity profile, their mode of administration, their expense and the increased level of supervision and education often provided to patients using these agents. Several recent quantitative studies including systematic reviews have explored these factors through analysis for statistically significant associations [15–18], though this approach is limited to pre-specified potential correlating factors. However, minimal qualitative research has been done targeting factors contributing to adherence with the newer biological agents [19]. Qualitative analysis has the potential to provide rich insights into a complex associated behavioural phenomenon that might not have been previously considered [20]. Qualitative approaches also have the potential to generate hypotheses gleaned directly from the subjects involved and are complementary to quantitative approaches. While qualitative studies of patients' experiences and attitudes may indirectly provide insights [21, 22], there is a lack of studies designed specifically to understand contributors to non-adherence. Understanding factors contributing to non-adherence may provide insights into potential interventions to improve this barrier to effective healthcare.

The aim of this study therefore was twofold. Firstly, we attempted to quantify patient adherence to rheumatic medications in a cohort of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) who were attending a specialized biologics clinic. We then attempted to gain an understanding for the reasons for poor compliance through analysis of patient interviews with the purpose of gleaning insights which could be amenable to intervention. To the best of our knowledge, there are no other qualitative studies examining factors impacting adherence in the biologics era from a clinical perspective.

Methods

Quantifying adherence and collection of demographic data

Study participants with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) were recruited from a specialized biologic clinic in a tertiary public hospital (Repatriation General Hospital in Adelaide, South Australia). All participants were on biologic therapy, and many were also on concomitant conventional disease-modifying anti-rheumatic drugs (cDMARDs). Consecutive patients from July to December 2016 were invited to participate in the study, and informed consent was obtained. Patient information collected and included in the study included age, gender, employment status, level of education, country of birth, ethnicity, religion, rheumatic condition, disease duration and all medications. Sample size was determined pragmatically with all patients agreeing to be involved in the study over the 6-month period included in the quantitative analysis.

Adherence was measured using the Compliance Questionnaire Rheumatology (CQR). The CQR is a 19-item questionnaire that has been developed and validated specifically to measure medication compliance in a rheumatology outpatient setting [8, 23]. A cut-off of 80% has been used to define satisfactory adherence which is consistent with previous similar studies [11, 24, 25]. Chi-squared tests were performed using STATA (SE 15) to compare differences in mean adherence (as measured by CQR) and the variables of interest. A 5% level of significance was considered statistically significant.

This study complies with the Declaration of Helsinki, and ethics approval was gained from the Southern Adelaide Local Health Network Ethics Committee (approval number HREC/16/SAC/22).

Patient interviews

Purposive (non-random) sampling was used to select patients for interview. Patients who were identified from the survey results as poorly compliant or those previously identified as poorly adherent by the treating team were invited to interview. Semi-structured interviews were performed by telephone by the primary researcher and audiotaped. Questions were based on themes and factors which have been found to be related to non-adherence in previous studies (Table 1) [4, 5, 12] and may be amenable to intervention. Additionally, patients were encouraged to raise issues that they identified as relevant to their own poor compliance. Audiotapes were transcribed verbatim and notes were also taken by the interviewer during the interview process. The qualitative analysis was an iterative process using grounded theory [22, 26, 27]. Data was managed using NVivo 10 (QSR International) for systematic coding. Some

Table 1 Themes used as a starting point to guide patient interviews

- Beliefs about the cause of their medical condition and its severity
- Influence of family and peers
- Assessment of adherence
- Beliefs about medication and perceptions of different types of DMARDs
- Presence and impact of side effects
- Social support and financial factors
- Use and belief around alternative therapies
- Relationship with healthcare providers

dual coding was undertaken to ensure the validity of the process. Codes were then explored for patterns using interview notes as an adjunct to interpretation. The meaning was attributed to data based on literal content, frequency and context. Themes were then reviewed with the researcher who transcribed all the interviews to explore different perspectives and confirm themes to accurately represent the data set. The most prominent theories were considered major themes and could be generalized to the whole data set; other significant themes were considered minor. Interviews were continued until saturation was achieved. This was considered to have occurred after nine interviews.

Results

Patient group

A total of 250 patients were provided with the study information sheet and given the option to participate in the study, of these 123 patients completed the questionnaire. 59% of patients had rheumatoid arthritis, 27% had psoriatic arthritis and 15% had ankylosing spondylitis (Table 2). All patients were on a biologic agent with 50% of patients also being on cDMARD therapy. The majority of patients were born in Australia (63%), with the next most common country of birth being the UK (27%). There were no non-English-speaking patients in our cohort who had education and employment levels well above the Australian national average.

Measuring adherence quantitatively

Of the patients who completed the CQR, 72% were identified as adequately compliant (using a > 80% compliance cut-off as adequate) (Fig. 1). There appeared to be a trend toward better adherence in certain patient groups (male, younger age range and fewer medications); however, there were no statistically significant differences in adherence based on these variables (Table 3). There were also no significant differences in adherence based on administration route or dosing regimen.

Factors contributing to non-adherence obtained from patient interviews

Five major themes were elicited from the analysis of patient interviews.

> Theme 1: The presence and tolerability of active symptoms significantly influence adherence
>
> Patients tended not to prioritize medication taking until they had a recurrence of symptoms. Some patients waited for quite a significant recurrence, including joint swelling and reduced function, before taking their prescribed medication. Some individuals who noted no difference before and after their medication went long periods without it. These patients did not appear to display an awareness or understanding of the concept of disease activity or the consequences of uncontrolled active inflammatory joint disease.

"occasionally I get some swelling, and when that stops me from doing what I want to do then I'll have the injection"

> Theme 2: Concern regarding long-term side effects of biologics and methotrexate being perceived as particularly "toxic"
>
> Patients were quite concerned that biologics would have adverse long-term effects even though most of these patients tolerated their current biologics very well with no side effects. They perceived that all medications are harmful in the long term and that side effects were inevitable. Patients felt it was better to minimize or be without medications if possible, but had no choice but to take them due to the impact disease flare has on their function.

"Long term… sometimes I think like in 20 years' time are they going to be like oh you've got this now. Um I mean without it I'm stuffed anyway so I got I got no choice but to take it"

"I'm expecting it to have an effect in the future."

"I started worrying about the long-term side effects of being on a drug that lowers your immune system"

"I think it's better to be taking less medication of any sort of… for any reason."

Table 2 Demographics and medication usage within the patient group

N = 123	All	RA	PsA	AS
% of patients	100	59	27	15
Age mean (range)	58 (19–86)	61 (19–86)	55 (30–86)	49 (26–64)
Disease duration mean (range)	18 (2–56)	18 (2.5–56)	18 (3–46)	15 (2–40)
Gender (% F:M)	66:33	79:21	57:43	33:66
Employment Status				
Employed	60%	36%	58%	83%
Unemployed	15%	19%	18%	6%
Retired	22%	42%	21%	11%
Not Specified	2%	3%	3%	0%
Max Educational Level Achieved				
University	33%	29%	36%	44%
Trade school	15%	14%	18%	17%
High school completed	17%	19%	9%	22%
High school part	25%	24%	33%	17%
Not specified	9%	14%	3%	0%
Biologic DMARDS				
Etanercept	33%	22%	52%	44%
Adalimumab	21%	17%	27%	28%
Tocilizumab	20%	33%	N/A	N/A
Abatacept	7%	13%	N/A	N/A
Golimumab	8%	8%	6%	11%
Infliximab	6%	0%	12%	17%
Certolizumab	2%	3%	0%	0%
Rituximab	1%	1%	N/A	N/A
Ustekinumab	1%	N/A	3%	N/A
Tofacitinib	2%	3%	N/A	N/A
Conventional DMARDs				
Any cDMARD	50%	61%	45%	11%
2 cDMARDs	7%	10%	0%	0%
3 cDMARDs	1%	1%	0%	0%
Methotrexate	45%	53%	45%	11%
Other medications				
NSAIDs	8%	10%	3%	22%
Prednisolone	18%	26%	9%	0%

RA, rheumatoid arthritis; *PsA*, psoriatic arthritis; *AS*, ankylosing spondylitis; *DMARD*, disease-modifying anti-rheumatic drug; *cDMARD*, conventional disease-modifying anti-rheumatic drug; *NSAID*, non-steroidal anti-inflammatory drug

Patients had quite negative views regarding methotrexate which was perceived as particularly toxic, much more so than biologics. Interestingly, the administration of concomitant folic acid appeared to add to the perception of toxicity (needing to take another medication to counteract side effects).

"Methotrexate, I never felt well at all using that. It's like my body was being poisoned. I was just feeling run down all the time"

"Taking these tablets with the side effects and all the other stuff you have to take to make sure you don't actually do more damage to yourself"

Theme 3: Biologics are "life-changing" and superior to conventional DMARDs

Even patients who were poorly compliant were positive regarding their experience of commencing biologic therapy. They reported that they would recommend biologic therapy over cDMARDs when speaking to other patients. Some patients even
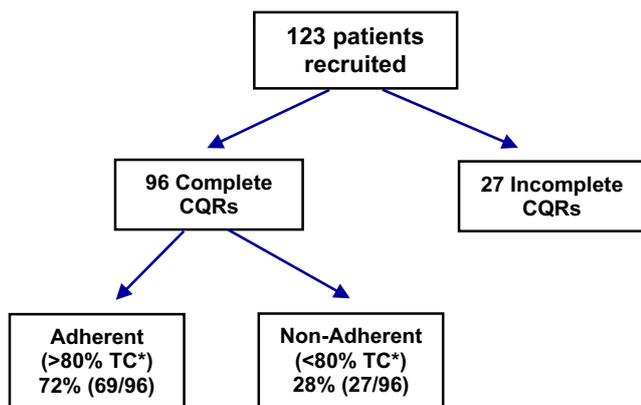
Fig. 1 Completion and results of the CQR used to measure the rate of medication adherence. CQR Compliance Questionnaire Rheumatology, TC taking compliance

perceived cDMARDs as simply a route to biologic therapy.

"Basically, I felt like I was in chains for 18 years and then the chains dropped off"

"They could tell…you know..the personality was calmer and happier and everything after he started on [biologic agent name]"

"So it was pretty much a miracle drug really"

"and boy it's fantastic and it's the best thing since sliced bread"

Theme 4: The relationship with the treating rheumatologist is pivotal in the patient's disease experience and adherence

A patient's relationship with their treating physician, whether positive or negative, was quite central in their experience of their condition and affected adherence. Some patients, when asked an open-ended question about their experience with their condition, talked specifically about their experience with each rheumatologist who had looked after them.

Patients reported becoming more adherent after discussion with their rheumatologist if they trusted them.

"those appointments are really important so if I have any questions I can ask him about it"

Conversely, some patients admitted to not telling their rheumatologist what they are taking if they have had a negative experience with them.

Table 3 Compliance Questionnaire Rheumatology (CQR) results in subgroups of interest

Subgroup	n	Adherent %[a]	p value
Condition			
RA	60	72%	0.99
PsA	21	71%	
AS	15	73%	
Gender			
Female	62	66%	0.091
Male	34	82%	
Medication type			
Biologics only	47	74%	0.58
Biologics + cDMARDs	49	69%	
Age			
18–35	8	88%	0.53
36–60	44	73%	
> 60	44	68%	
Number of medications			
1–2	47	79%	0.31
3–5	28	68%	
6–13	21	62%	
Employment status			
Employed	45	71%	0.97
Unemployed	17	76%	
Retired	31	71%	
Not-Specified	3	67%	
Max educational level achieved			
University	31	68%	0.69
Trade school/other tertiary	16	63%	
High school completed	17	76%	
High school part	22	82%	
Not specified	10	70%	
Disease duration			
1–5 years	15	67%	0.84
6–10 years	25	68%	
11–20 years	27	78%	
20–56 years	28	71%	

[a] Adherent defined as > 80% taking compliance

"When I go to him I lie. I tell him what he wants to hear."

Theme 5: Diet, exercise and stress play a critical role in disease causation, flares and treatment

Patients frequently attributed both their initial disease causation and flares to changes in diet, exercise and stress. These factors were perceived to be central to disease pathophysiology and treatment to the extent that some patients believed that they would not require medications if they were able to optimize these factors.

"about '94 I had my first breakdown and that, I guess emotional stress…to me that worked on the rheumatoid… And then I sold my farm and got out of my job,

I was a stock farmhand in a small farm, and sold our house in Mt Gambier and moved up to Noosa that's where I swam and I had pressure off me and I seemed to come good"

Minor themes

Several minor themes were also identified. Developing habitual patterned behaviour was a challenge for some patients. Affordability was an issue for some despite biologics being heavily subsidized in Australia. Depression and social conflict were intermittent barriers to adherence, and needle phobia was reported by some as a rationale for minimizing injections. A preference for alternative therapy and distrust of "synthetic medications" was reported by some. Patients had an awareness of the high cost of biologics to the public healthcare system, and intriguingly, a minority reported that this contributed to them reducing the frequency of injection, out of a sense of social responsibility, to minimize costs to the community.

Discussion

Using the CQR, our study found a satisfactory adherence rate of 72%. This is considerably higher than that in many other studies [5, 28]. However, considering our patient population and clinic environment (namely highly educated patients, all native English speakers in a highly supported specialist biologics clinic including access to a rheumatology nurse) this result was considered to be surprisingly poor to the treating rheumatologists.

Limitations of the CQR in our cohort include that it does not differentiate between different medications but rather generalizes about a patient's adherence to their "anti-rheumatic medications". One CQR item is specific to oral medications (dose organizer use), and some items are dependent on patients' experiences when missing doses (which may not apply to a patient who has never missed a dose) leading to some incomplete surveys. This study was not adequately powered to truly determine whether there was a significant difference in adherence between various groups (based on demographic data). However, the study was designed with the intention of exploring factors which contribute to non-adherence using the interview data rather than the quantitative data to provide richer insights into this area with the intention of highlighting potential areas for intervention.

In our study, different patterns in non-adherence to biologics were reported which potentially could affect the impact of an individual's non-adherence. These patterns often fluctuated over time in an individual patient based on changes in their beliefs, disease course and social circumstances. Some

patients increased the interval between their biologic administration whilst they remained asymptomatic. Some research suggests that this behaviour might actually be preferable in some individuals by minimizing overall dose exposure and costs, and disease activity may not increase in selected patients spacing out biologics [29, 30]. However, other patients stayed off the medication until they had signs and symptoms of active synovitis, a strategy likely to have adverse long-term consequences. Therefore, recognizing a patient's pattern of non-adherence is critical to determining its consequences and to counsel the patient accordingly.

The first major theme noted in our study was that the presence and tolerability of active symptoms significantly influenced adherence and that patients self-titrated medications based on their symptoms. It has been well established in adherence literature that there are higher levels of non-adherence in the treatment of asymptomatic disease [13, 14]. Previous studies of patients with rheumatic diseases have confirmed that reducing symptoms leads to increase adherence [2, 8]. A qualitative study on rheumatoid arthritis patient perspectives suggested that patients initially try to self-manage flares in order to regain control and only seek medical attention after they feel they are losing control [31]. It has also been found that when patients feel an increased sense of control over their treatment they have improved levels of adherence [15] suggesting a shared decision-making approach may be effective. Our study population of poor compliers did not generally display an awareness or understanding of the concept of disease activity or consequences of uncontrolled active inflammatory joint disease. Increased belief in medication necessity and perceived effect are associated with good adherence, so it is reasonable to infer that patient education in this area is required [8, 15, 32].

Study participants voiced concern regarding side effects. This issue has previously been identified as being correlated with poor adherence [15]. Beliefs about the overuse of medications have also been linked to adherence [32]. However, it was particularly interesting that even though most patients had never experienced any side effects from their biologics, they still held a strong belief that future adverse effects from biologic medication were inevitable.

Even non-adherent patients felt biologics had a massive impact on their quality of life and were superior to conventional DMARDs. They reported that they would express this when speaking to other people with their condition highlighting the importance that these perceptions can have on influencing the patient group; potentially making other patients more likely to distrust conventional DMARDs. Patients appreciated the cost of biologics and felt privileged to have access to heavily subsided treatment. Previous studies have highlighted that higher cost of medication adds to its perceived value [21].

The importance of having a good relationship with one's treating rheumatologist and increased health professional support has been strongly linked to adherence in the literature [2, 14, 15, 32]. This emphasizes the need for shared decision making and may also provide support for the role of a specialist rheumatology nurse practitioner [33].

Despite using biologic DMARD medications, our study found that patients still felt strongly about diet, exercise and stress playing a critical role in disease causation, flares and treatment. Some patient's had the perception that if these factors were controlled there would be no need for DMARD therapy; hence, this belief greatly affects adherence. The links between factors such as stress, diet and exercise and the development and perpetuation of autoimmune disease have been explored in the literature. Stress may contribute to development and flares of autoimmune disease, dietary links have been suggested, particularly in their effect on the gut microbiome, and exercise is thought to counteract inflammation during flares of disease [34–37]. Another factor which is frequently reported to be associated with adherence is the concept of self-efficacy [25, 38, 39]. This is defined broadly as the belief that one's current health behaviours will impact future health. The belief that medication is necessary to treat rheumatic disease is strongly correlated with adherence [4]. The belief that lifestyle changes may alter health more than medications could therefore have an impact on adherence. The perception of alternative therapy as an option also influences adherence to conventional medication [40].

Limitations of the qualitative aspect of this study include the fact that the principal researcher is a clinician which could affect her perspective as well as the participants' responses. Care, however, was taken by the researchers to "bracket out" their perceptions and presumptions as is common practice in this study method [27, 41]. On the other hand, a level of knowledge of the patients' experience, treatments, healthcare system and disease process was useful to be able to relate to the participants and contextualize information [20, 22]. While patients were aware that they were talking to a clinician, interviews were conducted over the phone rather than in the clinic setting and care was taken to use "layman's" terms and to stay in the interviewer role even if patients asked a medical question. This method appeared to be effective as patients' responses were quite candid and open.

Our study population was all English speaking with high levels of education and employment, and we did not find that socioeconomic factors played a major role in adherence. However, in more ethnically diverse and economically disadvantaged patients, socioeconomic factors such as financial costs and transportation play a role [42]. The study was conducted in a single centre with relatively small sample size.

Factors contributing to non-adherence can be divided into intentional and unintentional factors (such as financial issues or language barrier). In our study, intentional factors were the predominant drivers for non-adherence. That is, our patients made a risk-benefit analysis based on their beliefs which guided their choice not to take their medications as prescribed [8]. Even in socially diverse communities, medication beliefs are more powerful predictors of adherence than clinical or sociodemographic factors [4].

Non-adherence was intentional and driven by patient beliefs and the patient's relationship with their rheumatologist also influenced adherence, both suggesting that shared decision making is critical to managing non-adherence.

Themes of intentional non-adherence also suggest that patient education is critical in improving adherence given it is driven by their beliefs. However, few interventional studies using patient education have been performed and results are mixed [43–45]. Given the common use of social media and the increasing use of patient support groups mean that common perceptions may have a strong effect [21]. Conversely, these platforms may provide an opportunity to enhance adherence.

Potential areas for educational interventions to improve adherence highlighted by this study include the pathophysiology of disease, concept of disease activity and consequences of active inflammation and long-term safety of DMARDs. Other potential targets of intervention include improving the relationship with the treating rheumatologist and in some patients managing concomitant mental health issues and socioeconomic stressors.

Conclusion

Measurement of adherence is challenging, and multiple factors contribute to non-adherence. This study focused on a particular group of closely managed, English-speaking, highly educated patients and identified predominantly intentional factors driving non-adherence. Optimizing adherence is essential to improving patient outcomes in rheumatic disease, and the emergent themes in this work suggest that enhancing patient education and shared decision making could improve adherence.

Compliance with ethical standards

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