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Patient Perspective on Decisions to Switch Disease-Modifying Treatments in Relapsing-Remitting Multiple Sclerosis

1. Introduction

The treatment and follow-up of people with relapsing-remitting multiple sclerosis (pwRRMS) have transformed substantially [1], shifting from relapse management to altering the disease course with Disease-Modifying Treatments (DMTs) [2]. In this new therapeutic paradigm, pwRRMS' experiences of treatment decisions are multiple and complex. RRMS is chronic and progressive; treatment goals change with time, and in more advanced phases different trade-offs become more relevant [3]. Neurologists are now required to support decisions at various times during the relapsing disease course with limited evidence [4] and they do so with explicit concerns about DMTs risks [5].

The science about switching DMTs is still developing [6] despite the large cohorts of pwRRMS with long-term experience of several DMTs. Studies about switching mostly focus on clinical outcomes (e.g.[7-10]) and few studies focus on DMT

decision-making from the perspective of pwRRMS [11]. This article presents results from a qualitative study investigating how pwRRMS weigh up the pros and cons of DMTs. We examine how pwRRMS perceptions about DMT effectiveness and risks change when switching is needed and new treatments are considered.

2. Methods

Design, sample and analysis strategy

A qualitative study of 30 semi-structured interviews with pwRRMS in England was conducted to explore their decision-making process around DMTs, including essential reasons for starting, stopping, or switching DMT. 16 participants had switched DMT and their experiences were compared with those who had only ever taken one DMT or none. Of those 16, eight participants had taken two or more DMTs; eight had taken three or more. The median number of DMTs was two (Table 1). This qualitative study was part of a project to develop an evidence-based patient centred decision aid [12], which included evidence of pwRRMS needs identified through systematic reviews [3,13], in-depth interviews [11], and surveys using discrete choice experiment methods [14]. Participant eligibility criteria were: clinician confirmed diagnosis of RRMS; aged 18+; signed written informed consent. MS specialist neurologists in a referral centre in a teaching hospital in the north of England (United Kingdom) were asked to identify pwRRMS meeting study criteria. They were then approached by a research nurse and once consent was obtained, they were

contacted by a qualitative researcher (IE) to arrange the interview. 42 pwRRMS were identified, nine declined because of work commitments or lifestyle reasons and three could not be reached. A purposive sampling strategy [15] guided by a theoretical framework developed through a critical interpretative systematic review of the literature and published elsewhere [13] was employed. We aimed to include heterogeneous DMT experiences (treatment naïve, experience with specific DMTs, people who decided to switch or stop DMTs) but allowed for flexible criteria to capture and refine emerging knowledge. For example, after conducting the first ten interviews, new significant clinical or psycho-social factors were identified such as: women of fertile age; experience with DMTs with risk of progressive multifocal leukoencephalopathy (PML); within one year of diagnosis; in full-time employment. In this way, while the sample size was small, the sample composition was sufficiently diverse, providing a reasonable mix of demographics, disability status, DMT intake and experiences of administration routines and side effects, ensuring that theoretical saturation was achieved [16].

[Insert Table 1]

Interviews using semi-structured topic guides lasted 45-90 minutes and were conducted face to face (n=22) in the participants' homes or their preferred venue (public space, private room in the hospital, etc.), or by phone (n=8). All interviews were audio-recorded, transcribed verbatim and analysed using a thematic analysis [17]: initial coding by theme was done by the same qualitative researcher who

conducted the interviews (IE).Sub-themes were further developed and coded by two qualitative researchers (IE, AM) with NVivo (©QSR) international qualitative analysis software. These sub-themes were grouped into two broader categories or meta themes specific to pwRRMS with switching experience, by cross-referencing individual accounts with the group of switchers and then the entire data set. Meta-themes were refined through regular discussions with the wider research team (BP, HB, HF, SP), which included a pwRRMS (GP).

Ethical approval was obtained from the NHS Health Research Authority (IRAS: 199646).

3. Results

Decisions to change DMTs were influenced by a combination of clinical and psycho-social outcomes. Negative clinical outcomes were iatrogenic adverse events (i.e. renal and hepatic disorders), heightened risk of progressive multifocal leukoencephalopathy [18], presence of antidrug/neutralizing antibodies and new disease activity combined with availability of new DMTs. Psychological (fears, anxiety) and social outcomes (convenience, interference in daily life) seemed equally relevant.

Two meta-themes were identified: a distinctive, rapid and emotional decision-making process, and a different impact of communication for escalation or de-escalation.

3.1 A distinctive, rapid and emotional decision-making process

3.1.1 Revisiting old emotions: Switching DMT and MS prognosis

Participants often found switching DMT hard, feeling "devastated", scared, anxious and "worked up", echoing similar emotions to those reported at diagnosis [11] because it implied a disease and/or a treatment routine transition. People worried about an unknown treatment with uncertain effectiveness, new side effects and long-term risks. Mainly, however, they were concerned about how this necessary change may relate to MS prognosis and how the number of DMTs available on the list were decreasing. These feelings were present even when current treatments had not been tolerated well. Deborah (aged 42) explained her emotions when she had to stop her first DMT after developing liver complications:

> *"I was devastated because I'd been on Interferon for so long. Obviously, I didn't like that I had to inject myself every day. It was painful and I've got skin problems, indentations in my buttocks from injecting, and in my thighs all lumpy. I didn't mind stopping it for that reason. But I was really worried that I was gonna have a really big relapse."*

Conversations about changing DMTs were recalled as being initiated by physicians, often followed by direct recommendations of which treatments to have next. A small number of participants reported taking the initiative of stopping DMTs because of intolerable side effects but, in general, pwRRMS adopted successful strategies to adhere to treatment routines, enduring side effects by adapting daily activities. Those needing to stop DMTs because of tolerability often felt they were not listened to sufficiently by clinical teams, who were perceived as overlooking discomfort by not facilitating fast access to other available DMTs. Nevertheless, participants who asked to switch experienced the change of medication in positive terms. Sheila

(aged 27) explained how she changed treatment because she developed anticipatory pre-treatment anxiety after two years of weekly injections:

> *"I just hit this block. And I felt sick doing it. I'd just start feeling anxious on Tuesdays knowing it was coming up. The thought of doing it for the next 50, 60 years, it's just like, 'I can't do this'. So when they said I could go on tablets, it was just so much better for me."*

Initiatives to stop DMT temporarily were also commonly reported by younger female pwRRMS because of pregnancy planning. They often resumed the same DMT shortly after delivery, depending on disease activity and breastfeeding plans. Nevertheless, for these women, time frames without a DMT were long even with quick conceptions. For example, Suzie (aged 30) stopped her DMT for 20 weeks before trying to conceive. Although conception happened after eight weeks, she did not resume DMT during pregnancy or for another 12 weeks post-delivery, adding up to a total of 18 months without a DMT. Suzie had two relapses during conception and a further relapse eight weeks after delivery. In our sample, participants reported that clinical teams discussed evidence on risk of relapses at pre-conception, pregnancy and post-partum [19] with fertile age women before they had expressed explicit conception plans. Seemingly comparable discussions about reproduction plans were not reported by male participants.

3.1.2 A distinctive and often faster decision-making process

The strategy to start pwRRMS on the next DMT without delays after experiencing clinically relevant relapses often resulted in the deferral of in-depth conversations until after the new medication had already been initiated. Conversations about

switching due to clinical factors were often described as rushed and lacking depth with some participants being told over the phone which treatment they were going to take next. In general, pwRRMS did not seem to question or discuss switching recommendations at length, as they had done with their first DMT choices [11]. Deborah (aged 42) explained how she was told to change DMT after developing a liver dysfunction:

> *"Not a lot of discussion really because they wanted to get me back on to a drug quite quickly, before I'd started having any more relapses. So it was quite a quick decision. The MS nurse just rang me and said, 'Obviously you need to stop the Interferon. And Glatiramer Acetate is the only other drug you can have, so that's it.' I don't even think I saw her in clinic. I think she just arranged to come to the house with all the information and went through it. […] Unlike the Interferon I didn't go into it in depth or anything. I just listened to what the MS nurse said. I looked briefly online about the drug. And, I just thought, 'Well, I've got no other choice'…*"

Whilst good clinical practice, which included a home visit, was illustrated here, shared decision-making differed between the first and second DMT on the patient side (less research time, perception of reduced choices) and for the MS teams (less in-depth discussions).

In RRMS, DMT successive decisions occur in a distinctive "dynamic decision-making process" [20] where a number of interdependent actions are taken over time (including potentially several DMTs) with an overall long-term goal (delay disability).

In contrast, the decision environment (clinical, psycho-social) changes both spontaneously and as a consequence of earlier decisions.

3.2 A different impact of communication for escalation or de-escalation

At the time of fieldwork in England, DMTs were ranked hierarchically by clinical guidelines and funding eligibility criteria [21] making access to the newest DMTs conditional on disease activity (relapse frequency and severity). The treatment selection was guided by an NHS England algorithm [22] and the treatment strategy most commonly experienced by participants was escalation based on sequential DMT prescription; ineffectiveness of a first-line DMT was followed by the prescription of a second-line DMT [23]. This approach influenced communication experiences in successive DMT decisions. DMTs placed at the end of the sequential list were portrayed as more effective but having major, potentially fatal side effects, whilst those at the start were presented as less effective, mainly with minor temporary risks. However, pwRRMS can experience a major impact on their lives from these minor risks that can drive them to stop treatments. Similarly, iatrogenic adverse outcomes requiring stopping DMTs were reported by five of our participants across a range of first-line and second-line DMTs (Table 2).

[Insert Table 2]

Influences of the sequenced prescription approach on communication experiences differed depending on whether the person was: going forward on the list (escalation); going backwards (de-escalation/de-risking); or taking the last DMT available on the list.

3.2.1 DMT effectiveness and safety while moving up the escalation ladder

In switching DMT decisions, the set of available options was narrowed down further by new negative clinical outcomes, funding criteria and clinical judgement. In this process, pwRRMS' perception of choice was also reduced. People who had already taken several DMTs seemed aware of the sequenced prescription strategy and this helped them to accept switching recommendations with little questioning:

> *"It was a question of, which is the next drug on the list. And Fingolimod was offered."* (Kimberley, aged 48).

Explanations about why a new DMT was needed and how this related to disease advancing were recalled as being vague, and at times, contradictory. The three measures used to assess disease activity [24] (Table 3) were discordantly interpreted by different physicians.

[Insert Table 3]

For example, for Daisy (aged 27), the neurologist seemed to consider relapses a measure of disease progressing, but not of medication failure, despite still suggesting changing DMT:

> *"I'd got the optic neuritis and my consultant said, 'It's not that the Fingolimod isn't working at all but considering you've had a relapse on it, do you want to switch to something else?'"*

Although this may had been because there was a reduced annual relapse rate compared to pre-treatment, interpreting effectiveness can be challenging for pwRRMS and clinicians when relapses and brain lesions are used simultaneously to assess DMT failure.

Radiological features in precise space and time are increasingly used to manage MS [24]. For instance, with Georgia (aged 56), the neurologist considered brain lesions a measure of DMT failure unrelated to relapses but related to uncertain MS prognosis:

> *"'We've found these lesions in your spine on the MRI scan,' my neurologist said, 'that for me means that you're not exactly having a relapse but it points to the fact that actually Teriflunomide is not working. You can carry on taking them, it's fine if you do. But I would prefer you to go on something stronger just to… make sure nothing else happens.' And he didn't tell me what that might be, what might else happen."*

At times, when participants considered or enquired about a DMT that did not follow the recommended prescription order, DMT safety was presented in oversimplified negative terms. Significantly, this risk presentation influenced participants' perceptions of certain DMTs that they were likely to take in the future because they were reserved for a more advanced stage of RRMS:

> *"When it came round to him [neurologist] actually suggesting I go on Fingolimod, I do remember thinking, 'Is this the drug you said that could kill you?' [laughs] And I think he was referencing the brain infections…as to why it could kill you. So that sounded quite scary initially. And then, suddenly, it was an option there on the table." (*Sam, aged 39).

Risk presentation of chances of serious adverse effects had to be revised when clinical judgement suddenly justified the use of these treatments. However, this did not escape the notice of pwRRMs, who recalled feeling fearful about the previous negative narratives of second-line DMTs.

3.2.2 De-escalation: Effectiveness and safety while going down the ladder

De-escalation - prescribing in the inverse sequential order - was mainly driven by safety factors and initiated by physicians. When pwRRMS replaced their DMTs with others perceived as being less effective than the ones they were currently taking, they followed recommendations to switch reluctantly, because of fears related to effectiveness and tolerability. These feelings, which were present in escalation switches, seemed even more intense in de-escalation. Catrina (aged 37) explained this:

> *"Natalizumab is quite effective and I was thinking, if I'm low or medium [risk], it's worth running the risk actually of staying on it because it's effective. I'm doing pretty well on it. I've got used to the routine. I don't wanna change drugs because then you've got this whole thing of, 'Oh, am I gonna tolerate it? What are the side effects gonna be?'"*

Occasionally, de-escalation was initiated by pwRRMS because of psycho-social factors. Daisy (aged 27) asked for a different treatment that did not require hospital administration when she started a new job so she did not need to disclose MS to her new employer:

> *"I never officially told work that I had that condition and I suppose in a way it's almost to hide it, 'cause if I'd stayed on the Natalizumab I'd have to take Friday morning off once a month … all the time. So I talked to my consultant about that and she said, 'We'll try you on Fingolimod'."*

Daisy explained, however, that if she had a big relapse while on the new DMT she would ask to restart Natalizumab. De-escalation was reported by five of our participants and it always involved participants changing from Natalizumab to Fingolimod.

3.2.3 Reaching the end of the escalation ladder: Taking the last DMT available

Those with high disease activity approached the end of the DMT escalation list faster because they were on second-line DMTs early on or, for those with longer disease courses, because they had already tried all of them. Mary (aged 45) had taken six different DMTs, when her physician suggested the last one on the list (Alemtuzumab):

> *"I wasn't having time to recover from one relapse going into the next, so that's when my consultant said I could think about Alemtuzumab which he said, 'It's sort of like the atom bomb of treatments for MS at the moment'.'. My husband said ''Well, she does not have a choice'"*

This quote illustrates how when the end of the escalation list was reached, some pwRRMs perceived this situation as a fallacy of choice: there was no alternative but to take this "last resort" DMT. Alan (aged 25), diagnosed at 17 years old, had already taken Natalizumab and Fingolimod when Alemtuzumab was suggested:

> *"After my brain scan being so bad that's when my consultant said, 'Look there's this one hopefully about to get approved'. So I knew there were nothing else for me. My back against the wall if you wanna call it."*

Despite safety concerns, since all the other DMTs were inappropriate or had failed to contain their disease, participants felt that they were left with no choice but to take this last treatment. Bruce (aged 30), diagnosed at 20 years of age, had escalated fast through two DMTs when Alemtuzumab was offered:

> *"I was a bit scared, like 'Where do we go from here?' and my neurologists told me about Alemtuzumab. It was an unlicensed drug [at the time], which I think scared me a little bit, but by that point I just thought 'Oh, give me anything, anything, any chance'…"*

For participants with high disease activity, understanding of risk was reasoned [25] through individual experiences of undesirable MS outcomes.

4.1 Discussion

This study demonstrated that despite the term "switching" implying that similar treatments are inter-changeable, for pwRRMS taking new treatments involves different emotions, routines, risks, prognosis and communication experiences. Most studies of pwRRMS' DMT decision-making explore first decisions where pwRRMS often have to choose between treatments they had not experienced or had heard little or perhaps nothing about. Studies [26] investigating patients' perspectives of switching DMTs also found that pwRRMS fear the uncertainty of new treatments. This study demonstrates that switching DMTs is emotionally demanding, partly because of the fear about transitioning to secondary progressive MS, partly because of the uncertainty of DMT effectiveness [13].

The relationship between patterns of prescription and pathology are still mostly unknown. Several effectiveness and safety questions remain about the sequential

use of immunoactive agents [4]. Few studies have explored how consecutive decisions are impacted by communication experiences with physicians. Information processed in first decisions about risks cannot be unsaid in subsequent discussions, and it is likely to influence future decisions.

In England, the National Institute for Health and Care Excellence (NICE) prescribing guidelines provide the decision framework within which the choice of DMT in pwRRMS needs to be justified [5]. However, overlap among eligibility criteria for specific compounds enable some discretion based on individual preferences, such as risk perception, comorbidities and other factors, as long as compliance with commissioning criteria can be demonstrated using the NHS' Blueteq system [27]. Although the NICE guidelines fundamentally provide an incremental therapeutic pathway, the real-world therapeutic pathway may often rather become cyclical with pwRRMS moving up and down the escalation ladder.

The concept of escalation vs early intensive treatment strategies rose from safety concerns over some DMTs [28] and current treatment algorithms reserve some second-line DMTs for higher disease activity. However, this strategy has direct impact on the perceptions of pwRRMS about DMTs. De-escalation is a strategy well described in other inflammatory diseases [29] and should be studied further in RRMS. Some DMTs have an increased risk of adverse effects the longer they are taken. For example, Natalizumab in pwRRMS who are positive for John Cunningham virus are at increased risk of PML [18], and de-escalation/de-risking strategies have been proposed [30] Ocrelizumab is another example, since it can lead to hypogammaglobulinaemia and impaired vaccine responses [31,32] Although de-escalation/de-risking generally refers to switching from second to first-line agents

[33,-34], for pwRRMS a change between second-line DMTs may also feel like "de-escalation" and rightly so given efficacy data vary not only between first and second line DMTs but also among them. With new DMTs becoming available, this may apply to other switches like from Fingolimod to Cladribine [35] and Ocrelizumab [36].

An in-depth understanding of patients' perspectives about DMTs is critical, since patients and physicians often have different values and priorities about treatments. This study presents a novel contribution to the field of treatment decision-making in RRMS by being the first one to demonstrate the relationship between different treatment decisions and how people's involvement in decisions vary across the disease pathway.

There are several limitations to this study. Qualitative studies are characterised by using small sample sizes to support the in-depth case-oriented analysis fundamental to qualitative inquiry [37]. Our sample was small, non-random and limited to patients recruited from a single centre, which may cause bias at a patient and neurologist level, since professional practices often become aligned within a centre. Findings are based on pwRRMS and physicians' recall of events and perspectives, which are not always an accurate reflection of the decision-making context, processes, and outcomes. However, our results indicate a pattern of decision challenges sustained over time impacted by physician communication, suggesting that more support is needed along care pathways. Given the general limitations of qualitative data, our analysis was systematic and rigorous but exploratory and hypotheses generating only. Future research efforts could test the validity of these in a larger sample from different sites.

4.2 Conclusion

All DMT decisions are interconnected and all treatment options need to be presented to people as appropriate. Information encounters with pwRRMS should not focus on individual decisions but on the complexities and uncertainties of moving from one choice to the next and what this can mean to people's lives.

There is a significant unmet health need to develop patient-centred decision aids that support decisions across the disease life course and changing reality of treatment goals in chronic and cyclical diseases such as RRMS. Decision aids support a more reasoned personalised choice that can be re-visited as circumstances change to support ongoing decisions across their lives [38].

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Table 1: Summary of participant demographics

	Total Number of Participants N= 30		
GENDER	**FEMALE**	**MALE**	
	22	8	
ETHNICITY	**WHITE**	**BLACK BRITISH (CARIBBEAN)**	**ASIAN BRITISH (PAKISTANI)**
	28	1	1

AGE	**18-25**	**26-30**	**31-45**	**46-56**
	2	10	12	6
AGE AT DIAGNOSIS	**15-25**	**26-30**	**31-45**	**46-56**
	12	7	8	3
DISEASE DURATION	**< 12 MONTHS**	**1-5 YEARS**	**6-10 YEARS**	**11-20 YEARS**
	4	10	11	5
DMT NUMBER PER PERSON	**0 DMT**	**1 DMT**	**2 DMT**	**3 OR MORE DMT**
	3	11	8	8
Total number of participants with Switching DMT experience N = 16				
GENDER	**FEMALE**	**MALE**		
	13	3		
ETHNICITY	**WHITE**	**BLACK BRITISH CARIBEANN**	**ASIAN BRITISH (PAKISTANI)**	
	15	0	1	
AGE AT DIAGNOSIS	**15-25**	**26-30**	**31-45**	**46-56**
	7	4	4	1
DISEASE DURATION	**<12 MONTHS**	**1-5 YEARS**	**6-10 YEARS**	**11-20 YEARS**
	0	3	9	4

Table 2: Participants who experienced adverse events

Name (Age)	DMT when adverse event experienced	Adverse Effects (self-reported)
Alan (25)	Alemtuzumab	Thyroid dysfunction
Catrina (38)	Natalizumab	Hepatic dysfunction caused pancreatitis
Deborah (42)	Betaferon	Hepatic dysfunction, needs to take immunosuppressant drugs
Monica (35)	Interferon B	Hepatic dysfunction
Sam (39)	Fingolimoid	Low white blood cell and liver enzyme dysfunction

Table 3. Measures to monitor disease activity in RRMS

3 RELATED MEASURES TO MONITOR DISEASE ACTIVITY IN RRMS			
	RELAPSE	BRAIN SCARRING	NEUROLOGICAL TESTS
NO DISEASE ACTIVITY (NEDA)[39-40]	No relapses	No MRI activity (new or enlarging T2 lesions or Gd-enhancing lesions)	No disability progression

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