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Jutta Richter, Aurelia Beichert, Tim Filla, Gamal Chehab, Jörg Distler, Matthias Schneider, Inna Frohne, D. Sert, M. Aslandag

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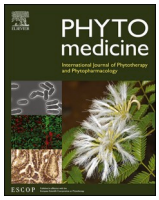

Original article

Recreational cannabis use is the driving factor for participation in medical cannabis trials in inflammatory rheumatic diseases

Richter JG [a,b,*], A Beichert [a,b], T Filla [a,b], G Chehab [a,b], D Sert [c], M Aslandag [c], JHW Distler [a,b], M Schneider [a,b], I Frohne [a,b,d]

[a] Clinic for Rheumatology, University Hospital Düsseldorf, Medical Faculty of Heinrich-Heine-University, Düsseldorf, Germany.
[b] Hiller Research Center, University Hospital Düsseldorf, Medical Faculty of Heinrich-Heine-University, Düsseldorf, Germany.
[c] Asepha Käthe-Kollwitz-Straße 60 04109, Leipzig , Germany
[d] Private practice for rheumatology, Essen, Germany

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ABSTRACT

Background: Though medical cannabis (MC) may have a role in the treatment of pain and anti-inflammation in patients with inflammatory rheumatic diseases (IRD), evidence and data are rare. We evaluated IRD patients' attitudes towards the setting of a clinical trial (CT) with MC as prerequisites for the design of a prospective study in phytopharmacological translational research.

Material and Methods: A survey was conducted using the innovative Chatbot app Asepha enabling patient-centered data collection. Data collected included sociodemographic and disease-related information, current pain levels, treatment satisfaction, health status, and knowledge about MC. Patients' willingness to participate in a MC CT and their concerns (e.g.fear of side effects/dependence) were assessed. Feasibility of Chatbot use was evaluated. R was used for data analyses.

Results: 250 IRD patients (67% female) were included. Despite high medication satisfaction (85%), more than one third was interested in MC CT participation, and additional 41% were potentially interested. Patients with previous recreational cannabis use were more likely to participate in a MC CT (OR 1.89). Furthermore, limitations in daily activities (OR 1.08), and bDMARD therapy (OR 1.43) increase the willingness. Lack of sufficient information about cannabis (67%), fear of side effects (40%) and dependence on cannabis (31%) are limiting factors for CT participation.

Conclusion: Chatbot use is feasible in phytopharmacological research. Three-quarter of our patients reported some interest in MC CT. Relevant predictors of interest were identified, with a history of cannabis use being the strongest. Understanding and controlling confounders seems crucial for successful planning and conduction of patient-centered future clinical trials in phytomedicine.

Introduction

Though humankind has long used the plant Cannabis sativa as a herbal remedy, broad use in modern medicine has not yet been established (Friedman and Sirven, 2017). Due to the medical cannabis (MC) legalization already in place in some countries, e.g., United States of America (USA) and Canada, as well as simplification of the prescribability (since 2017) and legalization (since April 2024) of MC in Germany, there has been an increasing demand for MC (Statista Market Insights, 2024). This demand is partially related to the analgesic effects of MC that are well acknowledged for a range of chronic pain conditions (Whiting et al., 2015, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), 2022).

Reported data show a rising interest for the use of MC also by patients with inflammatory rheumatic diseases (IRD), both for the treatment of chronic pain and for the inhibition of inflammation as an adjunct to established immunosuppressive therapy (Atalay et al., 2020, Hobbs et al., 2020, Piekarz et al., 2025). Recent German data support the existing data regarding the strength of the analgesic effects of MC (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), 2022, Poli et al., 2018, Arkell et al., 2023, Guillouard et al., 2021). Clinical observations suggest that MC may affect functional and psychological

* Corresponding author.
E-mail address: jutta.richter@med.uni-duesseldorf.de (R. JG).

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aspects of life as well as Health-Related Quality of Life (HRQoL) measured by the Short Form-36 (SF-36) highlighting its broader impact on patient-centered endpoints (Poli et al., 2018, Arkell et al., 2023). A meta-analysis published in 2021 evaluated 15 studies with 10,873 patients with rheumatic diseases (e.g., rheumatoid arthritis (RA), systemic lupus erythematosus, spondylitis, fibromyalgia) (Guillouard et al., 2021). It included self-therapeutic use and MC, as well as all forms of ingestion, in patients with former and current cannabis use. The meta-analysis showed the interest of these patients in MC (1 in 5 patients), especially for pain relief (ranging from 26-68% of the patients depending on the underlying rheumatic disease) (Guillouard et al., 2021).

In recent years, Cannabis sativa has attracted significant interest in phytotherapeutic research due to its complex array of bioactive compounds, including cannabinoids, terpenes, and flavonoids. These constituents interact synergistically, producing diverse pharmacological effects that hold potential for therapeutic applications (Russo, 2011, Booth and Bohlmann, 2019). Immunomodulatory effects of cannabidiol (CBD), and its effect on the janus kinase pathways highlight the potential as immunomodulatory agents and might therefore increase research interest (Peyravian et al., 2020). Experimental studies show that cannabinoids, particularly cannabidiol (CBD), can suppress cytokine production. In vitro data indicate that CBD reduces levels of TNF-α, IFN-γ, IL-1α, IL-6, and IL-17A . These effects are linked to decreased NF-kB activity, which controls pro-inflammatory gene expression, and possible activation of the STAT3 pathway, contributing to anti-inflammatory responses (Kozela et al., 2010, Watzl et al., 1991, Hobbs et al., 2020, Nichols and Kaplan, 2020).

Thus, cannabinoids demonstrate potent anti-inflammatory and immunomodulatory activities through the regulation of cytokine profiles and suppression of key inflammatory signaling pathways, thereby supporting their investigation in clinical settings (Russo, 2011, Nichols and Kaplan, 2020). However, studies that connect phytochemical analysis, pharmacological effects, and real-world patient outcomes are still limited and research on IRD and MC in (randomized) clinical trials (CTs) is still in its early stages, revealing an important gap in evidence-based phytotherapy. A very recent review emphasized again that it is essential to develop and expand clinical trials focused on phytotherapy to systematically establish knowledge about its safety and efficacy in patients with rheumatoid arthritis (Piekarz et al., 2025). While mechanistic insights are promising, translational success and the feasibility of CTs depend strongly on patient engagement and real-world acceptability.

Patients' attitudes toward phytocannabinoids play a pivotal role in shaping translational research within phytopharmacology. Resistance or acceptance among patient populations can significantly influence clinical trial recruitment, adherence to dosing models, and the perceived credibility of cannabinoid-based therapeutics. Positive attitudes and skepticism can accelerate or hinder translational progress. Understanding the attitudinal factors enables researchers to design studies that integrate psychosocial dimensions with pharmacokinetic modeling and safety monitoring frameworks, ultimately guiding more effective, patient-centered development of phytocannabinoid therapeutics aligned with phytopharmacological principles. Evaluation of IRD patients' attitude to and knowledge about MC thus seems essential for the (cost-effective) preparation and conduction of sustainable CTs in IRD. Therefore, we investigated IRD patients' attitudes towards a CT using MC via an innovative Chatbot app designed with a user-friendly interface, mirroring the communication style and design trends, e.g., of popular social media platforms that have been used for patient recruitment for clinical trials. Our analysis encompassed determining whether attitudes towards MC is potentially influenced by treatment satisfaction, pain level, health status, knowledge about MC, and other factors.

Material and methods

From 16th February 2023 until 15th December 2023 a voluntary survey was conducted as a cross-sectional study among consecutively approached and recruited patients with an established IRD from the rheumatology outpatient clinics at our tertiary center in Germany. Eligibility criteria were established IRD, $\geq$ 18 years of age, and sufficient knowledge of German.

We developed the applied questionnaire taking experiences from discussions with the authors from the PhytoVIS database into account (Gramliner et al., 2022, Wegener et al., 2021). It included single- and multiple-choice items, and numerical rating scales (0-10). The anonymous survey encompassed sociodemographic information, self-reported diagnosis, and immunosuppressive medication. Patients' age was recorded in five groups to guarantee anonymity (18-29, 30-39, 40-49, 50-65, and older than 65 years). Patients' global health, limitations in daily living activities, and pain were recorded on numeric rating scales (NRS, 0-10, 0 = good global health/no limitations in daily living activities; 10 = bad global health/ high limitations in daily activities), following quality assurance standards, e.g., of the National Database of the regional collaborative arthritis centers in Germany (NDB) (Albrecht et al., 2024, Thiele et al., 2024). Psychometric reliability has been reported for most of the national database items, demonstrating, for example, that the individual NRS within the RAID are valid, feasible, reliable, and sensitive to change when used separately (Ferraz et al., 1990, Duarte et al., 2021). We inquired patients' willingness to participate in a potential CT with MC. Furthermore, we assessed potential concerns (e.g., fear of side effects, dependence on MC) that might prevent patients from participating in a CT.

The questionnaire was recorded purely electronically and designed for this purpose in the innovative Chatbot app Asepha (Asepha GbR, 2024). The integration of social media-inspired elements within Chatbot aims to reduce barriers to participation and facilitate smoother communication with potential participants. By leveraging the features of familiar digital environments, the Chatbot app might enhance patient engagement, making the process of joining clinical trials more intuitive and less intimidating for users. The Asepha app was programmed using the open-source framework Flutter (Flutter.dev, 2025) and the programming language Dart (Dart.dev, 2025) enabling to publish the app for Android and iOS with just one programming code base. On the server side, the open-source Content Management System Directus is used (Monospace, 2023). Among other relevant issues this protects the data from public access, and users could only see and edit data for which they have appropriate authorization. This software runs on servers at the Amazon Web Services (AWS) location in Frankfurt. The front and back end are connected via a REST interface. Machine-readable data is transmitted encrypted over the internet. The app was available free of charge via Apple's App store and Google Play Store. The app initially stored the answers entered by the participants in encrypted form on the used device. When a user completed the survey, all answers were sent once from the app to the server and deleted from the collecting device. To guarantee security compliance and data protection issues the Chatbot app use for data capturing was approved by the relevant local data protection officer, partly because the provider has also made comprehensive information available. Also Chatbot app analytics were not recorded to guarantee protection issues. In accordance with the study protocol, the local data security officer advised that written informed consent was not required, and was thus not collected.

Our outpatients had the option of completing the questionnaire in the clinic using a clinic-owned iPad (version 9) or by completing the survey on their own mobile device by scanning a QR Code provided with a survey advertisement flyer in the clinic. When patients completed the survey on the iPad or their mobile device in the clinic, we asked them how satisfied they were with the technology used to complete the survey and how they liked the topic of the survey (Likert scale 0-10). Patients' responses were collected anonymously after completing the survey. The

answers were documented in a table and transferred to an Excel sheet with two pass verification to encompass data entry errors.

Ethical approval was obtained from the local ethic committee (local study number 2021-1709-andere Forschung erstvotierend). The study was registered to the German Clinical Trials Register (Identifier DRKS00030875, https://drks.de/search/de/trial/DRKS00030875;jsessionid=11C5495213EE1D0999983B4389F694B1 registered 16th December 2022).

Statistical computations including descriptive data and penalized ordinal regression (POR) used R Version 4.3.1. Predominantly descriptive statistics were executed. Values are expressed as valid percentages for discrete variables, or as mean ± standard deviation (SD), range, IQR or median for continuous variables. A penalized ordinal regression (POR) was performed. Differences in locations were tested via Chi Square and - where appropriate - non-parametrically (Wilcoxon signed-rank test, Mann-Whitney-U-test and Kruskal Wallis Tests). All statistical tests were performed two-tailed, p-values less than 0.05 were considered significant. As the individual patient needed to fill in answers to all questions to complete the questionnaire, no missing data needed to be handled.

Patient and public involvement

Patients and the public were not involved in the design, conduct, or reporting of our research. We will involve patient research partners in the dissemination of the results.

Results

A total of n=250 IRD patients (67% female) were included, and approximately 25% (n=83) of those invited to participate declined participation. Most patients were recruited in the clinic, and further 26 flyers were handed out to patients who, for various reasons, were unable or unwilling to complete the survey using the clinic's owned iPad. Download numbers were not retrieved to guarantee patients' anonymity. The survey of patients' satisfaction with the technology used to conduct the survey performed in the clinic showed that they were generally satisfied (mean 9.0; NRS 0 = not satisfied, 10 = very satisfied) and that they considered the survey topic generally interesting (mean 7.2; NRS 0 = not interesting, 10 = very interesting).

The majority of patients was 40 to 65 years of age (n=147 (59%)), see Table 1 which also lists more sociodemographic and clinical data. Most patients (n= 93 (37%)) self-reported RA. Forty six percent of the patients (n=115) were on conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and 11% (n=28) on (concomitant) biologic (b) DMARDs. While more than one third of patients (n=104 (42%)) was currently on nonsteroidal antirheumatic drugs, 7% (n=18) took opioids, and 5% (n=13) opiates as part of their pain therapy. Number of taken pain medication was 0.8 (±0.9, mean ± standard deviation). Number of (additionally) taken herbal drugs was 1.0 (±1.4). On average, women consumed more herbal drugs (1.2 (±1.4) vs. 0.6 (±1.2)), and more pain medication (1.0 (±1.4) vs. 0.6 (±1.2)) than men. With mean numbers of taken pain medication and herbal drugs varying in disease groups the average number of herbal drugs taken was highest in patients with RA (mean 1.1 (±1.4)).

Former recreational cannabis use was reported by 17% (n=42), the distribution by disease groups is shown in Table 3. Former recreational cannabis use varied in age groups and was highest in the two youngest age groups, see Table 3. In addition, it was higher in male (n= 18 (22%)) then in females (n=23 (14%)). Current use of MC was at 1.2% (n=3, all male).

Thirty-five percent (n=88) of all patients were interested in participating in a CT with MC, while further 41% (n=103) were undecided. Only 24% (n=59) denied clinical trial participation. Interest in such a CT was only slightly higher in female (n=60 (36%)) than in men (n=28 (34%)).

Table 1
Sociodemographic and clinical data and interest to take MC in a clinical trial (n. a. not applicable, Conventional synthetic disease-modifying anti-rheumatic drugs (DMARD) = csDMARD, biological DMARDs = bDMARD, targeted synthetic DMARD = tsDMARD).

		Interest to take medical cannabis in a clinical trial		
	Total cohort	Yes	Undecided	No
Total cohort *n (%)*	250 (100)	88 (35)	103 (41)	59 (24)
Female *n (%)*	167 (67)	60 (68)	68 (66)	39 (66)
Age in years *n (%)*				
18-39	50 (20)	17 (19)	21 (20)	12 (20)
40-65	147 (59)	53 (60)	62 (60)	32 (54)
>65	53 (21)	18 (20)	20 (19)	15 (25)
IRD Diagnosis *n (%)*				
Rheumatoid arthritis	93 (37)	35 (40)	36 (35)	22 (37)
Spondyloarthritis	47 (19)	19 (22)	17 (17)	11 (19)
Connective tissue disease	62 (25)	20 (23)	29 (28)	13 (22)
Vasculitis	19 (8)	7 (8)	6 (6)	6 (10)
Others	29 (12)	8 (8)	16 (15)	7 (12)
Disease duration *(in years, mean ± standard deviation (SD))*	7.9 ±10.8	8.6 ±9.8	7.8±11.2	6.9 ±11.7
Current DMARD medication *n (%)*				
csDMARD	115 (46)	38 (43)	53 (52)	24 (41)
bDMARD	85 (34)	36 (41)	30 (29)	19 (32)
tsDMARD	9 (4)	3 (3)	5 (5)	1 (2)
No DMARD	41 (16)	11 (13)	15 (15)	15 (25)
Number of taken pain medication *(mean ± SD)*	0.8±0.9	1 ± 0.9	0.8 ±0.9	0.7 ±0.8
Number of taken herbal drugs *(mean ± SD)*	1.0±1.4	1.2 ±1.4	1.0±1.4	0.6 ±1.2
Pain (VAS 0-10, mean ± SD)	3.7±2.8	4.3 ±2.9	3.8±2.7	3.1 ±2.9
grouped *n (%)*				
No pain (0-3)	128 (51)	38 (43)	52 (51)	38 (64)
Moderate pain (4-6)	68 (27)	28 (32)	29 (28)	11 (19)
Severe pain (7-10)	54 (22)	22 (25)	22 (21)	10 (17)
Patient global health *(VAS 0-10, mean ± SD)*	4.7±2.5	5± 2.5	4.8±2.4	4.0± 2.4
Limitations in daily living activities (*VAS 0-10, mean ± SD)*	4.0±2.9	4.5 ±2.9	4.1± 2.9	3.1 ±2.7
Satisfaction with current medication *n (%)*	213 (85)	75 (85)	85 (83)	53 (90)
Former recreational cannabis use *n (%)*	42 (17)	26 (39)	12 (12)	4 (7)
Reasons for missing interest in a CT *n (%)*				
Not interested in studies	15 (6)	n.a.	2 (2)	13 (22)
Concerned of side effects	56 (22)	n.a.	41 (40)	15 (25)
Concerned of addiction	44 (18)	n.a.	32 (31)	12 (20)
Lack of information on cannabis	76 (30)	n.a.	69 (67)	7 (12)
Fear of cannabis	24 (10)	n.a.	14 (14)	10 (17)

About 42% (n=36) of (concomitant) bDMARD users were interested in participating in a CT with MC, compared to 33% (n=38) of csDMARD users.

Although 85% (n= 213/250) patients were currently (very) satisfied with their treatment, 75% (n=160/213) of them were (potentially) interested in the participation in a CT with MC. Currently (very)

unsatisfied with their treatment were 15% (n= 37) and 84% of these were (potentially) interested in the participation in a MC CT. Satisfaction with medication varied in disease, age, and medication groups, see Table 2.

The POR depicted that former recreational cannabis use (OR 1.89), number of known effects of MC (OR 1.50), current bDMARDs therapy (OR 1.43), current csDMARD therapy (OR 1.23), pain (OR 1.1), and limitations in performing daily activities (OR 1.08) increased patients' willingness to participate in a CT with MC. Lack of information on cannabis (OR 0.51), fear of cannabis (OR 0.30), fear of addiction (OR 0.77), and fear of adverse effects of cannabis (OR 0.32) limited patients' willingness to participate in a MC CT. Satisfaction with current medication, number of taken pain medications, and number of taken herbal drugs did not influence patients' willingness to participate in a cannabis CT, see Fig. 1.

As the POR showed elevated ORs for bDMARD and csDMARD user corresponding clinical parameters were analyzed and showed similar characteristics: Eighty seven percent of (concomitant) bDMARD users (n= 74) were satisfied with their medication and 84% (n=71) had a low to moderate pain levels. In addition, 39% (n=33) of (concomitant) bDMARD patients reported a (very) good general health status, and 46% (n=39) had no or little limitations in performing daily activities. In csDMARD users 84% (n=97) were satisfied with their medication, and 84% (n=97) had low to moderate pain levels. In addition, 40% (n=46) reported a (very) good general health status, and 46% (n=53) had no or little limitations in performing daily activities.

Patients who were undecided about MC CT or denied MC CT participation conveyed several predefined reasons, see Table 1. The primary concern for patients who were undecided about taking MC in a CT was the lack of sufficient information about cannabis (n=69 (67%)). Other relevant reasons were fear of side effects (n=41 (40%)), and fear of addiction on cannabis (n=32 (31%)). Furthermore, n=15 (6%) patients were generally not interested in participating in studies, see Table 1.

Gender differences emerged in concerns about addiction. Men (22%) were more likely than women (16%) to express worries about addiction. Among those who reported fear of addiction, we found that more women than men had severe pain (61% vs. 5%), and were slightly more often in a worse overall health status (30% vs. 27%)

Table 2
Satisfaction with current medication (conventional synthetic disease-modifying anti-rheumatic drugs (DMARD) = csDMARD, biological DMARD = bDMARD, targeted synthetic DMARD = tsDMARD).

	Satisfaction with medication	
	very satisfied / satisfied *n (%)*	rather unsatisfied / unsatisfied *n (%)*
Total cohort	213 (85)	37 (15)
Gender		
Female	138 (83)	29 (17)
Male	75 (90)	8 (10)
Age groups		
18-39 years	37 (74)	13 (26)
40-65 years	128 (87)	19 (13)
> 65 years	48 (91)	5 (9)
IRD Diagnosis		
Rheumatoid arthritis	83 (89)	10 (11)
Spondyloarthritis	39 (83)	8 (17)
Connective tissue disease	49 (79)	13 (21)
Vasculitis	17 (90)	2 (10)
Others	25 (86)	4 (14)
Current DMARD medication		
csDMARD	97 (84)	18 (16)
bDMARD	74 (87)	11 (13)
tsDMARD	8 (89)	1 (11)
No DMARD	34 (16)	7 (19)

Table 3
Former recreational cannabis use in gender, age, and disease groups.

	Former recreational use	
	Yes *n (%)*	No *n (%)*
Gender		
Female	23 (14)	144 (86)
Male	18 (22)	65 (78)
Age groups		
18-39 years	17 (35)	31 (65)
40-65 years	22 (15)	124 (85)
> 65 years	3 (6)	49 (94)
IRD Diagnosis		
Rheumatoid arthritis	13 (14)	78 (86)
Spondyloarthritis	8 (17)	38 (83)
Connective tissue disease	10 (16)	51 (84)
Vasculitis	4 (21)	15 (79)
Others	7 (24)	22 (76)

The statement of fearing addiction to cannabis was influenced by several factors. Patients with prior recreational cannabis use were less likely to fear dependence (OR 6.6, p=0.02), and the proportion of patients expressing fear of addiction tended to decrease with patients' increasing age (OR 0.7, p=0.04). Patients taking more pain medication exhibited lower the fear of addiction (OR 0.7, p=0.2). Conversely, more patients who reported that they had not enough information about MC were afraid of dependence (OR=4.4, p=0.001).

A correlation analysis revealed a phi coefficient of 0.16 (95% Confidence Intervall (95%CI) 0.1-0.3) between previous recreational cannabis use and fear of addiction. A lack of information on MC and recreational use was associated with a phi coefficient of 0.13 (95%CI 0.1-0.3).

Discussion

Besides a broad public interest in MC evidence on its use in IRD is still rare, and controlled prospective studies are urgently needed. Evaluation of IRD patients' attitude to MC thus seems essential for designing the most effective randomized controlled clinical trials. To the best of our knowledge, this is the first study assessing the interest of IRD patients in German rheumatic outpatient clinics in participating in a CT with MC. The study aims to unfold prerequisites for successful clinical phase II/III trial in the translational research of phytocannabinoids, enabling their optimal planning, execution, and evaluation. Additionally, an innovative Chatbot App is employed to facilitate patient-centered data collection. This tool efficiently gathers relevant patient information with minimal effort, enhancing both the accuracy and timeliness of data acquisition. Its innovation lies in its ability to engage patients interactively, personalize the data collection processes, and seamlessly integrate into clinical workflows, thereby improving patient experience and optimizing healthcare delivery and research. The survey mode is valued, but interest in data donation via download on patients' own mobile device is low.

More than three-quarters (76%) of our participants are (potentially) interested in a trial with MC. Of these, nearly 40% report former recreational cannabis use, while former cannabis use in the complete group is 17%, and 20% in those aged 18-65. These numbers are higher than those of the general German population aged 18-64, where recreational cannabis use is estimated at 8.8% (Bundesministerium für Gesundheit, 2024b, Deutsche Hauptstelle für Suchtfragen, 2023).

Regarding gender related and social aspects, studies report that women usually make greater use of the healthcare system (Bertakis et al., 2000), and women prefer the use of complementary and alternative medicine more than men (Zhang et al., 2015). We also show a higher mean herbal drug intake in our female patients (mean number of taken herbal drugs in females is 1.2 (±1.4)). Regarding the *recreational use of cannabis* our data show a higher percentage in males (22%) than in

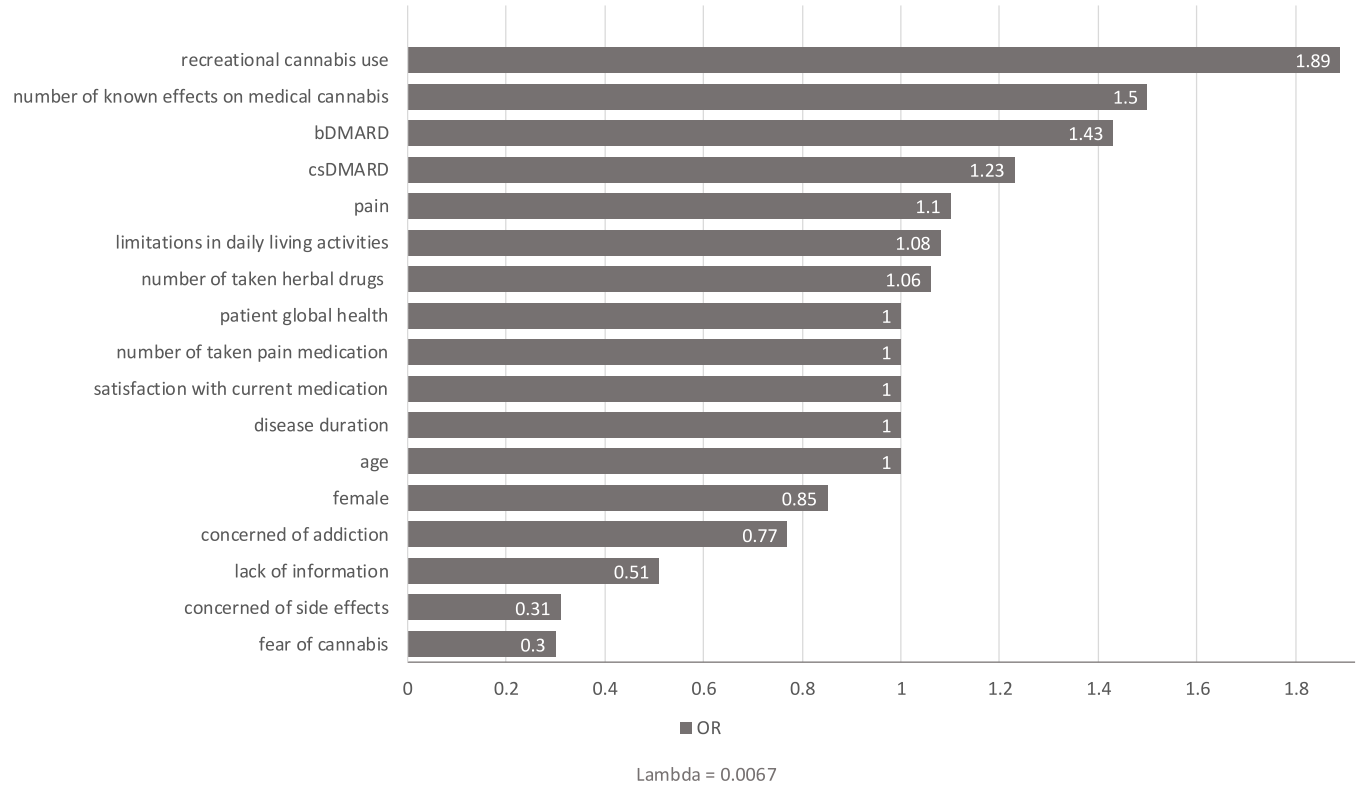

Fig. 1. Odds ratios of a penalized ordinal regression (with lambda 0.0067) (conventional synthetic (cs) disease modifying drug (DMARD), biological (b) DMARD).

females (14%), which is almost twice as high as the numbers of the general population in Germany (10.7% in males, 6.8% in females) (Bundesministerium für Gesundheit, 2024a). Recreational cannabis use in our patients may not be perceived as a form of alternative medicine but rather as part of a risk-oriented male lifestyle. This interpretation aligns with a study showing that men are more likely to 'abuse' cannabis than women and have a higher rate of dependence (Delforterie et al., 2015). In addition, a potential recall bias in self-reported prior cannabis use might exist in our patients.

Wall et al. report from 36.309 patients that within the group of cannabis users, men show more often a consumption of MC *(59% vs. 41%)* as well as non-MC *use (62% vs. 38%)* (Wall et al., 2019). In our cohort, the current use of *MC* is at 1.2 %, and both female and male IRD patients showing similar percentages. Current use of MC in our cohort is also comparatively low compared to Canadian data from Rampakakis et al., reporting 20.4 % current use or use within the last 2 years in individuals receiving conventional therapeutic care for rheumatic diseases (mostly rheumatoid arthritis (RA) and osteoarthritis patients) (Rampakakis et al., 2023). In contrast to our data, the study indicates that the use of MC by patients with RA is twice as high as that of the general population. The use is linked to worsening illness, discomfort, and prior recreational use (Rampakakis et al., 2023). Boehnke et al. depict that the use of MC in patients with rheumatic conditions is mainly due to inadequately treated symptoms (Boehnke et al., 2023). A cross-sectional survey among German patients taking cannabinoids reveals that most patients report their therapy with cannabinoids as more effective than their pain medication (Fischer et al., 2023). Our penalized ordinal regression (POR) also shows that reported pain and limitations in activity of daily life - which can both be regarded as a proxy for inadequately treated symptoms – influenced patients' willingness in a MC CT. However, it must be considered that our patients are generally satisfied with their antirheumatic medication and overall have low pain levels. In this context, our patient-reported pain level data are regarded as representative for German IRD patients, as low pain levels have been reported from the National Database of the regional collaborative arthritis centers in Germany in the last years (Albrecht et al., 2024, Thiele et al., 2024). From patients' perspective, a lower interest in non-established therapies therefore seems prudent. Although we analyze the (concomitant) bDMARD and csDMARD users in more detail, we are not able to detect reasons why patients with csDMARD and (concomitant) bDMARD therapy show higher ORs in the POR. This indicates a need for further research.

In the German noninterventional accompanying survey for the prescription of MC flowers or cannabis-based medicines at the expenses of the statutory health insurance, more patients with former recreational use are treated and reported (Schmidt-Wolf, 2021). In line with these findings and the results from (23), we show that our patients' interest in participation in a CT is associated with (former) recreational use. In addition, women are only slightly more interested in a CT with MC. This information may be helpful for the planning of future MC CTs and other studies, e.g., for planning the number of cases and the inclusion and exclusion criteria, as recruitment processes for clinical trials are known to be often complex, less effective, long-lasting, and costly (Kakumanu et al., 2019).

Many of our patients are hesitant or undecided whether they want to participate in a CT with MC because they are afraid of potential side effects (OR 0.31), while the number of known effects of MC increases interest (OR 1.50). However, side effects are reported to be generally mild (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), 2022, Whiting et al., 2015). According to the Federal institute for Pharmaceutical and medical Devices (BfArM) most treatment discontinuations (38.5%) result from lack of effectiveness, and only a minor part of patients stop treatment due to side effects (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), 2022). This data needs to be reported to our IRD patients and could then encourage more IRD patients to consider participating in a potential CT. Patients' long-term study participation in MC CTs and or registries would be of great value as data on long-term effects, comedication, optimal dosage, and intake form of MC, economic aspects, and specific impacts on IRD remain inconclusive, highlighting the need to provide reliable information for

physicians and concerned patients (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), 2022, Schmidt-Wolf, 2021).

Also, an Australian observational survey in patients with 20 qualifying medical conditions shows statistically significant improvements in Health-Related Quality of Life (HRQoL, assessed by the SF-36) in the first 3 months due to MC (Lent et al., 2024). Our patients' interest in MC CT is not influenced by patients' global health (OR 1.0) but by pain (OR 1.10), and limitations in daily living activities (OR 1.08), factors that might influence HRQoL. But these positive HRQoL aspects of MC intake reported from the studies might be attractive to IRD patients and need further investigations as well as communications in the patient management processes.

To increase IRD patients' interest in MC and thus their willingness to participate in a CT with MC, the data to be generated (e.g., on effects and side effects of MC / cannabinoid, and other plant-based compounds from phytotherapeutic research translation) must be included in the subsequent information process and educational efforts. These efforts are particularly important for IRD patients whose hesitance is driven by lack of information or fear, but also for physicians who might be unfamiliar with MC and plant-based compounds' administration (Rampakakis et al., 2023). Strengthening patients' and physicians' education as well as raising awareness regarding medical cannabis as a phytopharmaceutical drug (e.g., via well-founded, reliable webinars, patient leaflets) is crucial to translate promising mechanistic and phytopharmacological insights into safe and evidence-based therapeutic applications.

Overall, our results allow for a more efficient recruitment strategy and the targeted collection of crucial data on MC efficacy, ultimately enhancing the study's quality and efficiency.

Limitations

Our data represent data from a tertiary center only. However, we cannot exclude a potential selection bias as patients with more positive attitudes toward digital tools or MC might have been more likely to participate. Studies show that smoking and low socioeconomic status increase the consumption of medical and recreational cannabis (Steinberg et al., 2022, Guillouard et al., 2021, Jeffers et al., 2021). To keep our survey within a tolerable length, socioeconomic status, smoking behavior, current recreational cannabis use, and comorbidities (e.g., osteoarthritis, depression, or sleep disorders) were omitted. We recommend adding these aspects in future studies on patients' attitudes using our questionnaire or a similar one. In addition, due to the survey's aims, we did not assess the benefits of medical or recreational cannabis use, which might have influenced patients' perspectives. The questionnaire did not assess self-reported reasons why IRD patients would participate in a CT with MC. Concerns of side effects, of addiction, fear of cannabis, and lack of information on cannabis were only assessed in those who denied or were potentially interested in a MC CT.

A chatbot-based survey is a new survey tool for patients; this might have hampered study participation and response behavior, and we cannot exclude a recall bias. We did not use a validated questionnaire but used standardized items that are collected within the National Database Germany (NDB), where applicable, and have shown sufficient psychometric reliability (Albrecht et al., 2024). As usability was not the scope of our study, we provide only limited data on the usability of the chatbot; usability should be addressed in further studies using the chatbot.

Cautious generalization of the results is required, especially for populations with different characteristics, such as social or economic marginalization, as, i.e., in developing countries. Therefore, studies in larger and diverse cohorts and different clinical settings over longer periods are warranted.

Conclusions

More than one third of IRD patients was already interested in the participation in a MC CT, and additional 41% were potentially interested. Relevant predictors of interest in a MC were identified, with a history of cannabis use being the best predictor in IRD patients. Thus, the design and conduct of a randomized clinical trial with MC seems feasible in IRD patients. However, the identified relevant confounding factors, such as history of cannabis use, which need to determine the exclusion/inclusion criteria of the CT, must be considered. High quality of care resulting in high values of treatment satisfaction in IRD patients may limit the effects of cannabis. Strengthening both patients' and physicians' education and awareness around MC as a phytopharmaceutical (e.g., via up to date, reliable webinars), is vital for bridging the gap between promising mechanistic and phytopharmacological research and its safe, evidence-based integration into clinical practice. Our study provides valuable evidence for the proper planning and facilitated enrollment of future MC trials in patients with IRD, and thus, the evaluation of plant-based therapies.

Data availability statement

The trial protocol, the statistical analysis plan, and the data supporting the conclusions of this article are available on reasonable request by the authors.

Ethics statement

The study was reviewed and approved by the Ethics Committee of Medical Faculty at Heinrich-Heine-University Duesseldorf, local study number 2021-1709-andere Forschung erstvotierend.

Author contributions

JR, AB, IF, GC, MS designed, performed, analyzed the study, drafted the manuscript, and analyzed the data. TF analyzed the data and drafted the manuscript. All authors contributed to the manuscript's revision, read, and approved the submitted version and confirm being the sole contributors of this work and have approved it for publication. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

CRediT authorship contribution statement

Richter JG: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **A Beichert:** Writing – original draft, Visualization, Resources, Project administration, Investigation, Formal analysis, Data curation. **T Filla:** Writing – original draft, Methodology, Formal analysis, Data curation. **G Chehab:** Conceptualization, Writing – original draft, Writing – review & editing, Methodology. **D Sert:** Writing – review & editing, Software, Resources, Methodology. **M Aslandag:** Writing – original draft, Software, Resources, Methodology. **JHW Distler:** Writing – original draft, Supervision, Resources, Project administration. **M Schneider:** Writing – original draft, Supervision, Resources, Project administration, Formal analysis, Conceptualization. **I Frohne:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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