Patients' Willingness and Perspectives Toward Chimeric Antigen Receptor T-Regulatory Cell Therapy for Inflammatory Bowel Diseases

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Background: Inflammatory bowel disease is a life-changing disease resulting from recurrent intestinal inflammation. Current therapies (eg, steroids and biologics) are associated with mild to severe side effects, and none provide a cure. Recent research has focused on genetically engineering gut-specific anti-inflammatory T-regulatory cells (CAR-Tregs) to control intestinal inflammation, a logistically and conceptually complex approach. The purpose of our study was to understand patients' willingness to try CAR-Treg given 2 hypothetical scenarios—in a clinical trial or as a new treatment.

Methods: We surveyed people living with inflammatory bowel disease about their willingness to try CAR-Treg. The online survey was developed using patient focus groups and associated literature. We recruited participants through email and social media. We used descriptive and inferential statistics to analyze closed-ended questions and inductive thematic analysis to analyze open-ended follow-up questions.

Results: Survey participants indicated high willingness to try CAR-Treg therapy in both a clinical trial and as a new treatment. Willingness to try was not correlated with disease state or medication history. Women were less likely than men to indicate willingness to participate in a clinical trial. Participants' reasons for being willing to try CAR-Treg therapy included the wish to change their current treatment and the calling to participate in research. Participants that were not willing to try CAR-Treg mentioned the lack of long-term data and the success of their current therapy.

Conclusions: This is the first study to our knowledge to investigate patient willingness to try CAR-Treg therapy. Our results demonstrate the promise of moving this therapy into clinical practice as most patients indicated willingness to try.

Lay Summary

We surveyed people living with inflammatory bowel disease about their willingness to try a new therapeutic approach currently developed in several research laboratories—chimeric antigen receptor-expressing T-regulatory cells—and found high willingness to try, independent of disease state or medication history.

Key Words: IBD, patient preference, regulatory T cell, chimeric antigen receptor, willingness to try

INTRODUCTION

Inflammatory bowel disease is the umbrella term for Crohn disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC; also known as IBD unclassified or IBDU). While disease presentation differs between the conditions and etiology is unclear,[1,2] disease symptoms are ultimately caused by recurrent flares of intestinal inflammation. IBD symptoms can include chronic diarrhea, bleeding, weight loss, and abdominal pain. Furthermore, patients with UC are at increased risk for colorectal cancer.[1,2]

In IBD, the balance between conventional T cells, which target pathogens, and regulatory T cells (Treg), which maintain tolerance to commensal bacteria, food- and self-antigens, is disrupted. This loss of balance results in a proinflammatory

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conventional T-cell response to components of commensal bacteria, which contributes to the intestinal inflammation.[3,4] Current treatments for IBD such as steroids and biologics aim to induce and maintain remission through anti-inflammatory or immune suppressive mechanisms. However, treatment targets are not gut specific and other tissues can be affected—current therapies are often associated with mild to severe side effects including headaches, fatigue, arthritis, serious infections, and blood cancer.[1,2] As a result of IBD symptoms and treatment side effects, people living with IBD report a significant reduction in health-related quality of life (HRQoL). This reduction is especially prominent in people with active disease and with chronic CD.[5,6] A recent systematic review on the effect of UC on well-being revealed that patients with active disease suffer from a clinically relevant reduction of HRQoL, while those with inactive disease scored comparable to the background population.[7,8] Similarly, it was found that active disease decreases HRQoL of patients with CD and receiving biologic treatment increased HRQoL compared to other treatments.[9] The impact of IBD on HRQoL and the lack of safe and effective gut-specific therapy underscore the need for development of new treatments.

Recent studies investigated the use of subsets of Tregs as a cellular therapy to stop and prevent the conventional T-cell response to commensal antigens and to reestablish the intestinal balance of Tregs and conventional T cells. Animal models and clinical trials have demonstrated the potential and safety of Treg therapy in IBD.[10] Major obstacles to a clinical breakthrough include technical challenges to obtaining sufficient numbers of Tregs (since Tregs are a rare cell population in human blood) and ensuring site-specific suppression of conventional T cells.[10–13] To overcome these challenges, we and other groups developed Tregs expressing chimeric antigen receptors (CARs), genetically engineered fusion proteins that are clinically applied in cancer immunotherapy.[14] CAR-Tregs can be designed to specifically recognize targets that are only present in the context of gut inflammation. This limits the potential for global immunosuppression and associated side effects as seen with biologic treatments. Proof-of-concept studies demonstrated feasibility of creating functional CAR-Tregs, and the risk associated with CAR-Treg therapy is anticipated to be similar to that associated with biologic therapy.[14–18]

CAR-Treg therapy is seen as promising approach to bring Treg therapy into clinical practice to treat autoimmune disease and prevent transplant rejection. However, since the treatment is conceptually and logistically complex, and includes concepts such as genetic engineering and virus, patients might perceive an unacceptable risk with this therapy.[19] While it has been shown that people with IBD accept medication risk in exchange for treatment benefit, some risks, particularly risks associated with new or unusual therapy, may not be acceptable to patients.[20,21] To address this knowledge gap, we surveyed people living with IBD to gauge their willingness to try CAR-Treg therapy. In the description of CAR-Treg therapy in the survey, we positioned CAR-Treg therapy as an alternative to injectable biologics. Our overall hypothesis was that people living with advanced stages of IBD or running out of treatment options (ie, receiving biologics) would indicate a higher willingness to try CAR-Treg therapy than would other people living with IBD.

METHODS

Survey Design

The survey was designed to understand the perspectives of persons living with IBD on this hypothetical therapy. We also created a brief description of the therapy using the analogy of forest fires for IBD flares. We described CAR-Treg cells as being like firefighters tasked with extinguishing inflammation/fire (hereafter referred to as "the firefighter analogy") to explain the new therapy to survey participants. The remainder of the survey consisted of questions based on our research questions and hypotheses.

We refined our draft survey using patient input and conducted 2 iterative focus groups using a semistructured interview approach to ensure the firefighter analogy and survey questions relayed the intended meaning (see Figure, Supplementary Data Content 1, which shows a schematic of our survey design process). In both focus groups, participants were asked to read the firefighter analogy and complete key draft survey questions. Participants then discussed their thoughts on CAR-Treg therapy, the firefighter analogy, and the meaning of the draft survey questions. The draft survey was revised before the second focus group based on feedback from the first focus group. Revisions included rephrasing to eliminate confusion, reframing of jargon, eliminating irrelevant questions, and adding new questions, one of which became our secondary outcome (described below). The final survey design was published online using Qualtrics.

Both focus groups were audio recorded and transcribed verbatim. We also collected participants' written responses to the draft survey questions. The focus groups were facilitated by J.V.S.

Primary Outcome Measures

We informed participants that we see CAR-Treg therapy as an alternative to injectable biologics and employed 2 primary outcome measures: (1) patients' willingness to try CAR-Treg as a new treatment after it has been established to work well, and (2) patients' willingness to try CAR-Treg in a clinical trial testing how well it works.

Patients' willingness to try CAR-Treg under the 2 hypothetical conditions was measured using a continuous rating scale anchored at 3 points using both numbers and phrases: (1) 0 "definitely not," (2) 50 "somewhat likely," and (3) 100 "I

would have definitely tried it." Survey participants were also provided an open-ended text box to share why they rated their willingness the way they did for the 2 outcome measures.

Secondary Outcome Measure

Our secondary outcome measure was participants' preferences over CAR-Treg fate after initial use. This secondary outcome measure reflects our interest in guidance for further CAR-Treg development—specifically, whether patients would want CAR-Tregs to remain dormant in their bodies, ready to be reactivated in a future flare of IBD, or prefer CAR-Tregs to be eliminated from their bodies after successful induction of remission. Participants were told that the former option included a possible long-term risk for the cells to change. In a follow-up open-ended question, participants were asked to share their most important consideration in choosing a preference over CAR-Treg fate.

Participant Recruitment

We aimed to conduct 2 focus groups with 5–8 participants each to inform our survey design. To recruit participants, we collaborated with the Gastrointestinal Society (GI Society) of Canada and advertised the study at an educational event and via posting on their web site. Due to illness and last-minute cancelations, we conducted the first group with 2 participants and the second group with 6.

Survey participants were recruited through 2 emails, 1 in English, 1 in French, to the emailing list, and 2 postings to the Facebook account of Discover Therapies, a Canada-based patient-driven group that aims to connect patients with ongoing clinical trials and focuses on IBD. We expected that there would be some overlap between individuals targeted in the email list and the Facebook group, but had no way to assess overlap between the 2 recruitment methods or to prevent people from completing the survey more than once. Survey recruitment occurred in October and November 2018 and the online survey was available between October 2018 and April 2019.

Statistical Analysis

We analyzed the survey data through descriptive and inferential statistics. The results for our primary outcome measures, willingness to try CAR-Treg therapy, were nonnormally distributed. To identify any demographic and disease-related factors that might contribute to the level of willingness, we used the nonparametric Mann–Whitney and Kruskal–Wallis rank-based statistical analyses and performed Dunn multiple comparison post hoc test to identify any difference in rank sums between groups. Due to the nonsymmetrical nature of our results, we report these as testing for difference between medians. We contracted age groups to reduce the number of age categories as well as levels of education to reduce the number of education categories. We conducted chi-square statistics to identify statistical significance of preference of cell fate compared to null hypothesis that there would not be a preference of cells to stay vs to be eliminated after reducing the flare. We used Prism 5, GraphPad Prism Software, Inc. for these analyses.

To analyze the influence of multiple independent variables on our primary outcome measures (willingness to try CAR-Treg therapy as new treatment or in a clinical trial), we conducted multiple linear regression analysis using SPSS Version 26, IBM. First, we conducted Shapiro–Wilk normality testing which confirmed that our dependent variables were not normally distributed with both outcome variables being negatively skewed with identified ceiling effect. As all independent variables were categorical, and most contained multiple categories, we created dummy variables for categorical independent variables. The regression analysis compared groups to a randomly assigned reference category (male, age 14–39, CD, never took immunomodulators or biologics, no IBD complications, preference of cells to stay after treating the flare, living in a rural community in Canada, highest education of high school or less). As missing values appeared to be at random, we deleted missing values pairwise to avoid reducing overall sample size. We tested for multicollinearity by using a matrix of Pearson bivariate correlations. We interpreted the intercept as conditional mean for this group and report the slope of our predictor variables as units increase or decrease of the conditional mean.

Thematic Analysis

Open-ended answers to survey questions were analyzed by inductive thematic analysis by J.V.S. Codes were created as new concepts emerged and related codes were grouped together into larger themes. Multiple codes were possible per answer and we selected exemplary quotes for inclusion in this manuscript.

Ethical Considerations

We pursued this study under ethics approval from the University of British Columbia Clinical Research Ethics Board (UBC CREB Number H17-01720).

RESULTS

Response Rate

The advertisement email was sent twice (once in English, once in French) to an average of 4798 subscribers and the Facebook posts reached 1922 people. The combination of the 2 recruitment methods were accessed by 1680 people (1603 from advertisement emails and 77 from Facebook posts; extent of overlap not known). Six hundred ninety-seven (697) patients participated in the survey (41% of clicks on recruitment links), with 534 patients completing the survey (32% of clicks on recruitment links; 77% of patients who started the survey).

Demographics and Disease History

The majority of survey participants identified as female, had more than high school education, and resided in Canada (Table 1). Participants came from all age groupings between 14

TABLE 1. Demographics and Disease History of Patient Participants

	n	%		n	%
Gender			Age at onset		
Female	354	66%	Years, mean (min, max)	24.8 (0, 75)	n/a
Male	176	33%	Age at diagnosis		
Other	0	0%	Years, mean (min, max)	30.1 (8, 75)	n/a
Missing data	4	1%	Interval diagnosis-onset		
Age			Years, mean (min, max)	5.3 (0, 56)	n/a
14–18	1	0%	Last symptoms		
19–29	95	18%	Within the last 3 months	402	75%
30–39	112	21%	3–6 months ago	39	7%
40–49	127	24%	6 months to 1 year ago	41	8%
50–59	104	19%	More than 1 year ago	52	10%
60–69	69	13%	Severity of last symptoms		
70–79	20	4%	Mean, scale 0–100 (min, max)	56.5 (0, 100)	n/a
80–89	2	0%	All IBD medication a patient has tried (multiple allowed)		
90+	0	0%	Corticosteroids	439	82%
Missing data	4	1%	5-aminosalicylic acid	426	80%
Education			Immunomodulators	294	55%
High school or less	74	14%	Biologics	325	61%
Some college/university	197	37%	Antibiotics	294	55%
Undergraduate degree	137	26%	Probiotics	322	60%
Graduate degree	119	22%	Exclusive Enteral Nutrition	138	26%
Missing data	7	1%	Other	70	13%
Community of residence			IBD complications (multiple allowed)		
Rural	132	25%	Abscess	127	24%
Suburban	214	40%	Fistula	150	28%
Urban	178	33%	Stricture	193	36%
Missing data	10	2%	Surgery	179	34%
Country of residence			Reported 1 complication	111	21%
Canada	289	54%	Reported 2 complications	89	17%
United States	183	34%	Reported 3 complications	52	10%
Other	62	12%	Reported all complications	51	10%
Disease			Did not report any complications	231	43%
UC	203	38%	Surgery because of IBD (multiple allowed)		
CD	312	58%	Resection	147	84%
IC	19	4%	J-pouch	11	6%
			Temporary ostomy	39	22%
			Permanent ostomy	17	10%
			Other	36	20%

Data are presented as counts and as percent of total respondents (n = 534) or as mean with minimum and maximum values.

and 79 years of age and resided in a variety of community sizes. The majority of participants reported having CD (58%). The mean age of symptom onset in our cohort was 24.8 years and mean age of diagnosis was 30.1 years (28 years for CD, 33 years for UC, and 31 years for IC). Most participants experienced their last symptoms within 3 months before responding to our survey. Over half (57%) of the respondents reported at least 1 IBD complication, and 37% reported more than 1 IBD complication with the most frequent complications being stricture and surgery. Most participants who had surgery had part of their bowel removed. As expected, most participants had tried first-line treatment while fewer tried second- and third-line treatments.

Perspectives on CAR-Treg Therapy

Responses from the 445 participants who completed the open-ended question about the firefighter analogy describing

the proposed CAR-Treg therapy fell under 3 broad themes (Table 2). The first theme was focused on the *promises of CAR-Treg therapy*. This included explicitly stating their interest, hope, and willingness to try the therapy. Other participants highlighted that they appreciated the personalized aspect of this therapy and a belief that this therapy would be better than their current medication.

The second theme focused on *concerns participants had with the CAR-Treg approach*. These included participants who thought CAR-Treg therapy sounded scary or mentioned concerns about the genetic engineering aspect of therapy development. Participants were also concerned about side effects in general, side effects caused specifically by the virus used, and mistakes during laboratory handling. Additional concerns included worries about cost or whether their insurance would cover the treatment.

The third theme focused on *participants' questions about the CAR-Treg therapy*. Participants wanted to learn more about the therapy—both in general and with respect to the specifics of the application, often related to time and amount. Other participants were interested in whether CAR-Treg therapy also treats systemic manifestations of their IBD, such as arthritis, and wanted to see more research done before making a decision regarding their willingness to try.

Preference on CAR-Treg Fate

When asked to choose between two options of what could happen to the cells after treating their flare, significantly

TABLE 2. Participants' First Thoughts and Concerns After Reading the 1-Page Firefighter Analogy

Themes	Representative Quotes
Promises	
Interesting	"It is an interesting concept."
	"I'm very interested, as this is not something, I am familiar with despite having done much research into Crohn's treatments, immunology, and inflammation."
Hope	"Great hope it will work."
	"Sounds too good to be true, but hope it is."
I want to try this	"No concerns. I'd try it today if were available."
Personalized therapy	"I would rather have my own cells rather than a synthetic drug or chemical fighting my disease."
	"To be designed specifically for me, great!"
Better than current treatment	"Everything would be better than Humira or Remicade."
	"I'm eager to find any type of treatment that works better than what I have had."
	"Sounds like less harmful side effects are possible than with current immunosuppressant therapies."
Concerns	
This sounds scary	"It sounds a little scary and futuristic."
Genetic engineering and genetically modified organism	"Introducing modified cells back into my body sounds like a bad idea. These cells make me think of genetically modified organism and the negative connotation surrounding them."
	"My concern is that the genetically engineered cells may trigger unknown illnesses in the patient."
Use of a virus	"I was concerned that the virus would not be contained to the inflamed area."
	"I would worry the virus would become active."
Mistakes during laboratory handling	"Concerned about getting blood injected back in me, what if it has not been stored correctly or properly labeled?"
Side effects	"That it will cause a inflammatory response that will end up making my Crohn's worse."
Cost and insurance coverage	"Sounds expensive."
	"Sounds great also sounds expensive, what are the other downsides besides cost?"
Open questions	
More information on therapy	"How long does it take to engineer and put the blood back into your body? How long does it take to start working?"
	"And how large of a dose of cells would it be? A vial? A pint?"
	"Do you need to redo this with every flare?"
More research needed	"What are some of the potential side effects? Is it possible that these cells could mutate/become harmful?"
	"Sounds promising but would like to see more research done."
Does this treat systemic symptoms	"I have systemic inflammation specifically IBD related arthritis. Would this treatment be able to help that as well?"

Data are presented as emerging themes and categories (indented) and representative quotes.

more participants indicated a preference for cells stay in their body in a dormant state, ready to fight a new flare when needed over having the cells eliminated from their bodies after successful induction of remission (57% and 39%, respectively; $P < 0.0001$).

When prompted to share their most important consideration in choosing CAR-Treg fate, those that indicated preference of cells to stay considered how debilitating their flares were; their wish to live flare-free; their worries that repeated treatment might lose effectiveness; their dislike of needles; their residence in a remote area; their concern around cost of treatment; their wish for improved quality of life; and their old age (Table 3). In contrast, those participants that indicated a preference for the cells to stop existing in their bodies highlighted that their flares were manageable; that flares were something known; the lack of long-term data on side effects; their worries about mutations; their young age; and that this was not yet a cure.

Willingness to Try CAR-Treg Therapy

When asked to rate willingness to try CAR-Treg therapy as a new treatment, participants indicated a median willingness of 93.5 [interquartile range (IQR) 82–100] (Fig. 1). Given the prompt to elaborate on why a certain level of willingness was chosen, respondents that indicated willingness to try highlighted the need to trust their gastroenterologist; the personalized nature of this therapy; the wish to change their current treatment, and their desperate wish for a cure (Table 4). Those that did not indicate willingness to try highlighted their concern about this being a new therapy, and the success of their current therapy.

Willingness to try CAR-Treg therapy in a clinical trial was significantly lower compared to willingness to try as new treatment ($P < 0.0001$) with a median of 77.5 (IQR 60–91) (Fig. 1). Respondents who indicated willingness to participate in a clinical trial highlighted the necessity of contributing to research and past experience with clinical trials. Additionally,

TABLE 3. Participants' Most Important Consideration for Choosing Their Preference of Cells Staying in Their Body in a Dormant State vs Cells to be Eliminated From Their Body

	Representative Quotes
Reasons for indicating preference for cells to stay in a dormant state	
Flares are debilitating	"Dealing with a flare is terrible and the thought of having a severe flare is scary."
	"I'd rather risk possibly side effects to not experience UC symptoms."
Wish to live flare-free	"Of course, I would love to be "cured" of my CD."
	"I want to try anything to help prevent the flare ups."
Worry about repeated treatment	"I have stopped treatment and started it again and not effective."
Dislike needles	"I don't like needles and want a normal life."
Living in remote area	"Because our remoteness having a flare up and waiting for cells would put a strain in my ability to work."
Cost of treatment	"The considerable cost of having to go in for multiple treatments."
Improved quality of live	"I am done with the years of pain and missing out on life."
	"So that I can live a normal life without worrying about my Crohn's 24/7."
Old age	"Flares are hard at my age."
	"My age, where "long-term" may be moot."
Reasons for indicating preference for cells to be eliminated	
Flares are manageable	"I can usually control my flare from progressing to an unmanageable state."
	"My flares are not usually so severe that I couldn't handle a bit of a wait."
Flares are something known	"Waiting for a next flare is how I live currently so I am okay with staying that way."
	"I'd prefer to stick with the known as opposed to the unknown."
Lack of long-term data on side effects	"Unintended long-term consequences that cannot be tested in the short-term."
	"Lack of information/longitudinal studies on the possible risks."
Worry about mutations	"Not knowing what the dormant cells might "change" into."
	"The risk of the cells changing/mutating into harmful cells in my body."
Young age	"I'm still relatively young, so the long-term risks concern me more than the inconvenience of repeated treatments."
No cure yet	"I just wish for a cure."

Data are presented as categories and representative quotes.

they highlighted their nonresponse to biologics and need for a new therapy; their worries about biologics; and the promise of site-directed personalized therapy (Table 5). Respondents who did not indicate willingness to participate in a clinical trial highlighted the success of their current therapy; the availability of other options for them, the wish for demonstrated long-term safety and efficacy and a general decision not to participate in research.

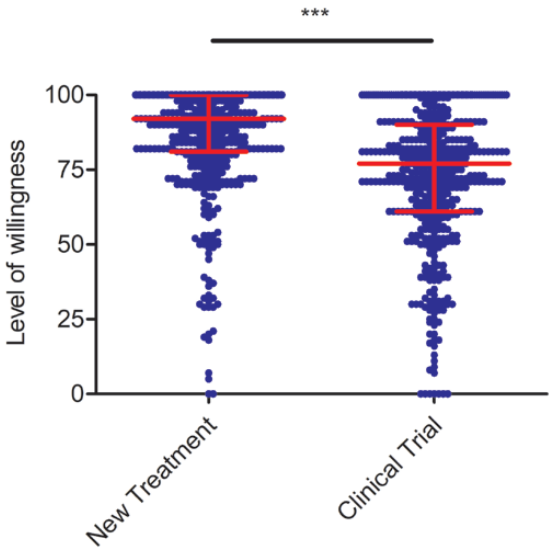

FIGURE 1. Willingness to try CAR-Treg therapy. Phase 4 indicates willingness to try CAR-Treg therapy as a new treatment that was shown to work well and is safe in people. Phase 2/3 indicates willingness to participate in a clinical trial to test the efficacy of CAR-Treg therapy after it has been shown to be safe in people. ***$P < 0.0001$.

Influence of Demographic Factors on Willingness to Try CAR-Treg Therapy

Overall, bivariate analyses did not identify clear demographic predictor variables for willingness to try CAR-Treg therapy in either scenario. As shown in Table 6 (new treatment), we observed a significantly higher willingness ($P = 0.0001$) to try CAR-Treg therapy in participants that indicated preference of the cells to stay (median 95, IQR 84–100) compared to those who preferred the cells to die after treating a flare (median 90, IQR 77–100). Furthermore, participants residing in other countries (median 100, IQR 89–100) indicated a significantly higher level of willingness ($H = 14.9$, $P = 0.006$) compared to Canada (median 91, IQR 77–100) and the United States (median 93, IQR 82–100). In line with the bivariate analysis, the multiple regression analysis identified preference of cells to stay and residence in another country as significant predictor variables and there was no significant effect of any other predictor variables on the willingness (see Table, column: new treatment, Supplementary Data Content 2, which shows the results of the multiple regression analysis). There was no correlation between any of the predictor variables (data not shown).

In contrast to what we found for willingness to try CAR-Treg as new treatment, our bivariate analyses on willingness to try CAR-Treg therapy in a clinical trial revealed a significant influence of gender. Females indicated significantly lower willingness than men (median 73, IQR 58–90 and median 80, IQR 71–91, respectively, $P = 0.0041$) (Table 6, clinical trial). In line with our findings on willingness to try CAR-Treg as new treatment, we observed a significantly higher willingness for participants who preferred cells to stay compared to those participants who preferred cells to die after treating the flare (median 80, IQR 68.25–93.5 and median 71, IQR 56.25–82, respectively,

TABLE 4. Participants' Reasons for Choosing Their Level of Willingness to Try CAR-Treg Therapy as New Treatment

	Representative Quotes
Reasons for indicating willingness to try as new treatment	
Trust in their GI doctor	"I trust my gastrointestinal doctor, he knows me."
	"I trust his [my doctor's] judgment; he hasn't steered me wrong yet."
Personalized nature of the therapy	"Specific to gut, made for me with my own cells."
Wish to change current treatment	"I am on a biologic and the side effects are scary."
	"[I want] to stop with weekly Humira injections."
Desperate wish for a cure	"I would try anything."
Reasons for indicating nonwillingness to try as new treatment	
Concern that this is a new therapy	"I'd be hesitant due to the newness of the therapy."
	"I have to be out of options before blindly taking something with no data proving long-term use."
Success of current therapy	"My symptoms are being managed well enough."
	"My present medication is working well and I experience little side effects."
	"I'd only use it after I fail biologics."

Data are presented as categories and representative quotes.

TABLE 5. Participants' Reasons for Choosing Their Level of Willingness to Try CAR-Treg Therapy in a Clinical Trial

	Representative Quotes
Reasons for indicating willingness to try in a clinical trial	
Calling to participate in research	"I would risk a long term flare up for the greater good."
	"Innovation is not possible without testing hypotheses."
	"I believe in supporting research, trying cutting edge approaches, and doing the best I can for my health."
Positive experience with participation in clinical trials	"I have had experience and success with clinical trials in the past."
Need for other treatment options	"I've already failed with all the biologics."
	"Humira stopped working and I'm having nasty side effects from the Remicade."
Worries about using biologics	"So many terrible known side effects of biologics."
Promise of site-directed personalized therapy	"More targeted than biologicals."
	"It is using my own blood cells to improve my health rather than a biologic."
Reasons for indicating nonwillingness to try in a clinical trial	
Success with current treatment	"Biologics have been keeping my Crohn's in check. Would not stop them unless necessary."
Availability of other treatment options	"Because I am not out of options. I can still use biologics which are proven safe to use."
Wish for demonstrated long-term safety and efficacy	"I would be a little hesitant not knowing if it works and taking a risk on the side effects."
	"I prefer more established medications that were tested for long time."
General unwillingness to participate in clinical trials	"I choose not to be a lab rat."

Data are presented as categories and representative quotes.

$P < 0.0001$). Furthermore, we observed a trend ($P = 0.0531$) that willingness to participate in a clinical trial for CAR-Treg therapy appears to decline with increased level of education. The multiple regression analysis corroborated these findings: female gender and preference of cells to stay were identified to have a significant impact on willingness to accept CAR-Treg therapy as a clinical trial while level of education was not significant (see Table, column: clinical trial, Supplementary Data Content 2, which shows the results of the multiple regression analysis).

DISCUSSION

To the best of our knowledge, this survey represents the first study to research willingness of people living with IBD to try CAR-Treg therapy. Participants indicated high median willingness to try CAR-Treg as treatment and slightly lower median willingness to participate in a clinical trial to test efficacy. Significantly more participants preferred CAR-Tregs to stay dormant in their bodies to prevent future flares compared to being eliminated with a need for renewed future treatment. In contrast to our hypothesis that willingness would be correlated with a more advanced disease state, and/or biologic treatment, we did not find any demographic or clinical parameters to predict willingness to try CAR-Treg therapy as new treatment.

Participant willingness to participate in a clinical trial for CAR-Treg was lower compared to trying it as new treatment, but higher than anticipated. Recent studies on motivations and barriers to participate in IBD clinical trials found similar and slightly lower levels of willingness to participate in hypothetical clinical trials.[22–24] These studies identified a clear correlation between advanced or active disease and willingness. We did not find similar correlations in our survey; however, participants that indicated willingness highlighted their need for other treatment options while those who did not indicate willingness highlighted the success they had with their current treatment and the availability of other treatment options. We found participants highlighting a calling to participate in research, a sentiment found throughout the IBD literature.[22–24] Furthermore, our respondents that indicated willingness to participate highlighted past clinical trial experience as a reason. While Gehrmann et al[23] and Larussa et al[22] reported a correlation between past clinical trial experience in IBD and willingness to participate, Ravikoff et al[24] found the opposite result. In line with Ravikoff et al's[24] findings, female participants in our survey were significantly less likely to indicate willingness to participate in a clinical trial. Studies in other clinical areas have also found gender differences in participation in hypothetical clinical trials with females less likely when side effects are unknown and when the research is not well explained.[25,26] Our scenario specified that the treatment was safe in people, however survey participants commented on lack of long-term safety data and we did not provide an explanation of the trial protocol.

Willingness to try a new treatment or participate in a clinical trial might be affected by thoughts, concerns, and

TABLE 6. Bivariate Analysis of Influence of Demographic Predictor Variables on Willingness to Try CAR-Treg Therapy Either as New Therapy (Phase 4) or in a Clinical Trial to Test Efficacy (Phase 2/3)

	New Treatment				Clinical Trial			
	Median	IQR	Min, Max	*P*	Median	IQR	Min, Max	*P*
Gender				*0.1102*				***0.0041***
Female	92	80.75–100	0, 100		73	58–90	0, 100	
Male	93	82.25–100	5, 100		80	71–91	8, 100	
Age				*0.9800*				
14–39	92	81–100	0, 100		73.5	59.75–97.25	0, 100	
40–69	92	82–100	0, 100		79	62.5–92	0, 100	
70–90+	91.5	79.75–100	60, 100		73	69.25–81	7, 100	
Education				*0.2432*				***0.0531***
High school or less	91.5	81.75–100	21, 100		81	61.75–92.75	9, 100	
Some college	95	82.5–100	0, 100		78	64.50–92	0, 100	
Undergraduate degree	92	80.5–100	19, 100		73.5	60–100	0, 100	
Graduate degree	91	79–100	18, 100		70	54.5–86.5	0, 100	
Community				*0.4329*				*0.1721*
Rural	94	82.25–100	20, 100		78.5	62–91	0, 100	
Suburban	92	81–100	0, 100		76.5	62–90	7, 100	
Urban	91	80–100	29, 100		72	57–90	7, 100	
Country				***0.0060***				*0.0817*
Canada	91	77–100	0, 100		75	60–89.5	0, 100	
United States	93	82–100	18, 100		76	60–91	0, 100	
Other	100	89–100	70, 100		81	71–94	0, 100	
Medications tried				*0.2983*				*0.3057*
Biologics	92	81.5–100	18, 100		78	61–90	0, 100	
Immunomodulators	90.5	71–100	0, 100		73	52–82.5	0, 100	
Other	94	82–100	0, 100		76	65–91	0, 100	
Complications				*0.8880*				*0.5675*
Yes	92	81–100	5, 100		78	61–91	0, 100	
No response	93	81–100	0, 100		76	60.25–89	0, 100	
Fate of CAR-Treg				***0.0001***				***<0.0001***
Cells should stay	95.5	84–100	7, 100		80	68.25–93.5	0, 100	
Cells should die	90	77–100	0, 100		71	56.25–82	0, 100	

Crosstab parameters include median, IQR, minimum and maximum values (min, max), and Mann–Whitney or Kruskal–Wallis *P*-values. Bold indicates significant (<0.05) or near-significant *P*-value.

understanding of that treatment. When we asked about participants' first thoughts and concerns after reading the firefighter analogy, participants mentioned concerns around mistakes in laboratory handling and that it involves genetic engineering and a virus. This could indicate a general mistrust toward anything created in the laboratory based on news reports and highlights the importance of avoiding sample mix-ups in hospital settings. Additional comments indicated a need for more refined educational material for patients once this therapy is ready for clinical application. This is in line with Veilleux et al's[27] report that patients' understanding of information provided by their physician resulted in reduced anxiety, and increased treatment satisfaction and adherence.[27]

Our finding that more participants preferred prevention of future flares while accepting long-term risk of the CAR-Treg cells to change is in line with previous reports which found that people with IBD were willing to accept an elevated risk of potentially serious side effects in exchange for an improvement of their IBD.[21] Furthermore, other research has demonstrated that people with IBD would accept long-term risk of serious side effects in exchange for an extension of remission.[20] Our participants further qualified their most important consideration for choosing a preference for fate by stating that "flares can be debilitating" and that they would "rather have risks than flares" after selecting a preference for CAR-Treg cells to stay dormant in their bodies. Those participants who preferred CAR-Tregs to be eliminated while accepting the risk of a future flare tended to indicate their ability to "manage their flare" and that their "flares are not too severe" and would thus have less clinical benefit from accepting the risk. These findings are in line with Johnson et al's report[21] that risk acceptance increases with clinical benefit.

We report our results as exploratory as we employed a convenience sampling approach and were unable to precisely identify our population of interest. While this limits the generalizability of our findings, the demographic, disease, and medication history of our participants matched clinical patterns across IBD for most characteristics. Our respondents reported a mean age of diagnosis of 28 years for CD and 33 years for UC. Previous studies found the peak incidence for CD and UC to be 20–30 and 30–40 years, respectively.[28,29] Thirty-four percent of our respondents experienced surgery and 84% of these were colectomies. Clinical observations reported rates of colectomy range around 25%–30% after 25 years of disease.[28] There is no sex difference in prevalence and incidence in IBD[30,31] overall, although UC is slightly more common in men while CD is more common in women.[28] Nonetheless, we received more responses from participants who identify as female. This skewing has been observed by others[32,33] and could be due to an increased propensity for women to talk about their health and seek health-related information.[34,35]

With respect to study limitations, our estimated survey response rate was 32% which is similar to previous IBD online surveys.[32,36,37] Since we were unable to rule out multiple openings of the email and Facebook post by individuals, the real response rate might be slightly higher. We also found that 30% of those who provided consent dropped out. We anticipated a high dropout rate because our survey encompassed 29 questions, multiple open-ended questions, and the 1-page written firefighter analogy. We also did not include questions about ethnicity and family income, which could influence willingness to try a new therapy. Finally, we did not meet the assumption of normally distributed data usually required to generate reliable results using linear regression analysis. We conducted regression analysis to identify confounders in the bivariate analysis rather than develop a predictive model, and the results corroborated the bivariate analysis. Furthermore, our survey results contained 34 records per independent variable, which is more than the various rules-of-thumb recommendations of 10–20 subjects per variable and far more than the recently identified 2 subjects per variable required to generate reliable results.[38] Given the exploratory nature of our survey, we were comfortable with conducting and interpreting the analysis.

CONCLUSIONS

Our findings support the continued development of CAR-Treg therapy for IBD, for autoimmune disease, and as therapy to prevent transplant rejection. In our exploratory survey, we found clear evidence for the acceptability of this treatment approach by patients, which indicates the feasibility of further therapy development. We suggest refining educational materials to address areas of concern around the process of creating CAR-Tregs and the application of the therapy, such as questions around dose and time of infusion and hospitalization. We further recommend continuous patient involvement throughout the stages of therapy development to ensure the final therapy would be accepted in clinical practice and to address patients' needs and emerging concerns during clinical testing.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Crohn's & Colitis 360* online.

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