




Mesenchymal Stem Cell Therapy Awareness, Knowledge, and Use for the Treatment of Fistulizing Crohn's Disease: An International Survey Among Gastroenterologists and Colorectal Surgeons

Paul Williams · Catherine Klersy · Chitra Karki · Dimitri Bennett ·

Ana María Rodríguez · Rachele Ciccocioppo 

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ABSTRACT

Introduction: Mesenchymal stem (or stromal) cells are a promising therapy for the treatment of various inflammatory and autoimmune diseases. This study aimed to understand awareness, knowledge, and perception of

Paul Williams and Catherine Klersy equally contributed to the study.

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P. Williams
Patient-Centered Solutions, IQVIA, Paris, France

C. Klersy
Service of Clinical Epidemiology and Biometry,
IRCCS San Matteo Policlinico Foundation, Pavia,
Italy

C. Karki · D. Bennett
Global Evidence and Outcomes, Takeda
Pharmaceuticals USA, Inc., Cambridge, MA, USA

D. Bennett
Adjunct, Perelman School of Medicine, University
of Pennsylvania, Philadelphia, PA, USA

A. M. Rodríguez
Patient-Centered Solutions, IQVIA, Madrid, Spain

R. Ciccocioppo (✉)
Gastroenterology Unit, Department of Medicine,
A.O.U.I. Policlinico GB Rossi and University of
Verona, Piazzale L.A. Scuro, 10, 37134 Verona, Italy
e-mail: rachele.ciccocioppo@univr.it

mesenchymal stem cells among gastroenterologists and colorectal surgeons, with particular focus on the perianal fistulizing Crohn's disease indication.

Methods: A web-based questionnaire was distributed to currently practicing and registered gastroenterologists and colorectal surgeons across 15 countries in North America, Europe, and Asia Pacific.

Results: Of 146 clinicians, 115 (79%) were aware of mesenchymal stem cells. The majority were moderately to largely interested in this therapy (87%), willing to use it in patients with perianal fistulizing Crohn's disease (82%), and believed it addresses unmet needs for these patients (93%). However, most responders reported having limited or no knowledge of this therapy (64%) or its efficacy (51%), safety (53%), and mechanism of action (65%) in perianal fistulizing Crohn's disease. Many clinicians (46%) also expressed concerns about using this therapy in these patients. Attending discussions and presentations on mesenchymal stem cells and seeing more patients with Crohn's disease were associated with increased awareness (both $P < 0.001$).

Conclusions: Many clinicians demonstrated an interest in mesenchymal stem cells in general and a willingness to use them to treat perianal fistulizing Crohn's disease, but this survey showed suboptimal knowledge of what mesenchymal stem cells are and how they work in this indication. This may explain clinicians'

concerns about use of this therapy and calls out for education activities.

Keywords: Mesenchymal stem/stromal cells; International survey; Perianal fistulizing Crohn's disease; Gastroenterologists/colorectal surgeons

Key Summary Points

Why carry out this study?

Mesenchymal stem (or stromal) cells (MSCs) are a promising therapy for the treatment of various inflammatory and autoimmune diseases, but their uptake in routine clinical practice is lagging behind.

An international survey was conducted to understand clinicians' awareness, knowledge, and perception of MSCs, with particular focus on the perianal fistulizing Crohn's disease indication.

What was learned from the study?

The majority of surveyed gastroenterologists and colorectal surgeons were aware of MSC therapy, were willing to use it to treat perianal fistulizing Crohn's disease, and believed it can address unmet needs for these patients.

There was a general suboptimal knowledge of MSC efficacy, safety, and mechanism of action, and many clinicians expressed concerns about using this therapy in routine practice.

The most common types of information requested to alleviate concerns were published data from clinical trials or real-world studies and conference or congress presentations.

INTRODUCTION

Mesenchymal stem (or stromal) cells (MSCs) are a heterogeneous population of cells with multilineage differentiation and anti-inflammatory or immunomodulatory activities. They are being intensively studied as a promising therapeutic option for treating inflammatory and autoimmune diseases [1–3]. MSC efficacy and safety in different disease areas, including fistulizing Crohn's disease, have been well documented in meta-analyses and systematic reviews of clinical trials [4–10]. Based on the evidence from clinical trials, regulatory approvals have been issued in different countries over the past decade. Allogeneic bone marrow MSCs received the world's first conditional approval in 2012 in Canada and New Zealand to treat children with acute graft-versus-host disease (GvHD) [11]. Since then, other sources of MSCs, such as those derived from adipose tissue and umbilical cord, have received full or conditional approval in South Korea, Japan, and India for different indications, including GvHD, fistulizing Crohn's disease, amyotrophic lateral sclerosis, spinal cord injury, knee articular cartilage defects, critical limb ischemia, and acute myocardial infarction [11]. Darvadstrocel is the first allogeneic MSC therapy approved in the EU, Israel, and Switzerland for the treatment of complex perianal fistulas in nonactive or mildly active luminal Crohn's disease [12–14]. It is a suspension of expanded human allogeneic MSCs extracted from adipose tissue, which can be injected directly into the fistula tracks to promote fistula healing through anti-inflammatory and immunomodulatory action [6].

Despite the general enthusiasm around the potential for MSCs to cure otherwise untreatable diseases, uncertainties have arisen among the scientific community regarding their use in routine practice, which may hinder this novel therapy from entering mainstream healthcare. Such issues include safety and efficacy concerns, knowledge gaps regarding their mechanism of action, and lack of optimized protocols for MSC isolation and ex vivo preparation for clinical use [2, 11, 15, 16]. In addition, regulatory, financial,

and reimbursement issues may reduce wide access to MSCs in many countries [17, 18].

These uncertainties raise potential challenges, including negative perception by healthcare stakeholders and patients regarding the efficacy, safety, and applicability of MSCs in the real world, despite approvals from regulatory authorities. Therefore, an international survey was performed to assess current awareness, knowledge, and perception of MSCs in clinicians who may be using or considering using this novel therapy in their routine practice. An exploratory analysis was also undertaken to identify factors associated with better awareness of MSCs. Given the approval of darvadstrocel in patients with perianal fistulizing Crohn's disease, this study mainly focused on this indication.

METHODS

Participants

This was an international, cross-sectional survey recruiting clinicians from 15 countries across Europe (Austria, Denmark, France, Germany, Italy, the Netherlands, Spain, Switzerland, and UK), Israel, Asia-Pacific (Australia, Japan, and South Korea), and North America (USA and Canada). Clinicians were identified from IQVIA's proprietary comprehensive database comprising both private and publicly available sources of data (e.g., OneKey healthcare professional database, Citeline, ClinicalTrials.gov).

Given the focus on the perianal fistulizing Crohn's disease indication, only registered gastroenterology specialists and coloproctologists or colorectal surgeons currently practicing in one of the selected 15 countries were included in the survey. To increase generalizability of the results, no specific exclusion criteria were applied. However, participants were required to be willing and able to read and complete a survey in English. For Japan only, both English and Japanese translated surveys were available.

All clinicians agreed to a data protection notice or website cookie policy electronically before being granted access to the survey. By agreeing to the data protection or cookie policy,

the clinicians consented to their data being used in the study unless they withdrew voluntarily afterward for any reason.

Survey Questionnaire

The survey was conducted through administration of an online questionnaire using the Qualtrics platform [19]. The questionnaire comprised a maximum of 37 multiple choice questions, developed on the basis of expert advice and a pragmatic literature review of studies collecting clinician perspectives in the broader stem cell field. Free-text fields were also included to allow clinicians to provide details to "other" options or provide explanations for their responses. In case a clinician preferred to receive a copy of the questionnaire via email, data were collected in this format and then manually uploaded into the electronic platform.

An overview of the types of questions included in the questionnaire is presented in Table 1 and the full questionnaire is provided in the electronic supplementary material (ESM). As clinicians were not compensated for this study, in order to encourage those who may not have heard of MSCs to complete the survey, a short set of questions was initially administered to all participants (full analysis set), regardless of their familiarity with this therapy. This included questions on clinicians' characteristics (e.g., age, experience, specialty, and practice setting) and their level of awareness of MSCs. Thereafter, only the clinicians who stated having limited, moderate, or strong awareness of MSCs (MSCs awareness subgroup) were asked an expanded list of questions regarding their use of MSCs in clinical practice and their interest, knowledge, and perception of this therapy. These clinicians were most likely to give valid responses to these questions.

Outcomes

The outcomes of interest for this study included level of awareness of MSCs, number of patients treated with this therapy, interest in the therapeutic field, willingness to use MSCs to treat

Table 1 Overview of the questionnaire administered to the participating clinicians

Clinicians' characteristics ^a	Practice setting (academic hospital, district general hospital, other)
	Primary specialty (gastroenterologists, colorectal surgeons)
	Age
	Duration of practicing years
	Attendance at conferences or congresses for gastroenterology or colorectal surgery in the last 2 years
	Attendance at discussions or presentations on MSCs in the last 2 years
	Number of patients with inflammatory bowel disease seen per month
	Number of patients with Crohn's disease seen per month
	Number of patients with perianal fistulizing Crohn's disease seen per month
Awareness questions ^a	Current awareness of MSC therapy (never heard, heard of it but don't know anything about it, limited, moderate, strong awareness)
Clinical use questions ^b	Already treated patients with MSCs
	Number of patients treated to date with MSCs
Interest and willingness to use questions ^b	Regularly keep up to date with developments in the MSC field
	Current interest in MSC therapy (no, minimal, moderate, large)
	Willingness to use MSCs in the clinical practice setting Explain why you are willing or not willing to use MSCs
Self-perceived knowledge questions ^b	Knowledge (no, limited, familiar, expert) of MSCs in general
	Efficacy in patients with perianal fistulizing Crohn's disease
	Safety in patients with perianal fistulizing Crohn's disease
	Mechanism of action in perianal fistulizing Crohn's disease
	Preparation or delivery in perianal fistulizing Crohn's disease
Objective knowledge questions ^b	Approved MSC therapy indications
	Term that best describes MSC therapy in general
	Term that best describes mechanism of action in patients with perianal fistulizing Crohn's disease

Table 1 continued

Perception questions ^b	Concerns for using MSCs in patients with perianal fistulizing Crohn's disease
	Information needed to alleviate concerns
	MSCs address unmet need for patients with perianal fistulizing Crohn's disease
	Explain why you think MSCs address or do not address unmet needs

MSCs mesenchymal stem/stromal cells

^aShort set of questions administered to all clinicians meeting the inclusion criteria (full analysis set)

^bExpanded set of questions administered only to the clinicians with limited, moderate, or strong awareness of MSCs (MSCs awareness subgroup)

patients with perianal fistulizing Crohn's disease, self-perceived and objective knowledge of this therapy in general and when applied to the perianal fistulizing Crohn's disease indication, and potential concerns with using MSCs in this indication.

Clinicians' characteristics, including clinical experience, were used to describe the sample and as potential predictors of increased awareness in the exploratory analysis.

Statistical Considerations

Descriptive statistics, including mean, standard deviation (SD), median, minimum, maximum, interquartile range, and number of observations (*n*) or percentages (%) and 95% binomial exact confidence intervals (CI), were used to describe the main study outcomes. Depending on the type of questions, the full analysis set or the MSC awareness subgroup was used as the denominator to calculate percentages, as appropriate. Where applicable, percentages within the MSC awareness subgroup were also calculated using the full analysis set as the denominator to extrapolate estimates to the population level. As missing responses were allowed throughout, the denominators varied among the different questions. Therefore, results for categorical variables are reported as number of events (*n*)/number of non-missing responses (*N*) and percentage.

In the exploratory analysis, univariable and multivariable logistic regressions were used to identify factors associated with increased

awareness of MSCs within the full analysis set. The dependent variable was awareness of MSCs, dichotomized as "never heard, do not know, or limited awareness" versus "moderate or strong awareness," while the covariates included geographic region (Europe, Americas, rest of world), type of institution (district general hospital, academic hospital, other), medical specialty (gastroenterologist, colorectal surgeon), number of years practicing (≤ 10 years, 11–20 years, > 20 years), attendance at any discussion or presentation on MSCs in the last 2 years (yes or no), and number of unique patients with perianal fistulizing Crohn's disease seen per year.

All analyses were performed using Statistical Analysis System (SAS) Enterprise Guide version 8.2 (SAS Institute, North Carolina).

Ethical Considerations

This study was approved by the New England Institutional Review Board (protocol number Alofisel-5006, 10 April 2020).

RESULTS

Survey Participants and Level of Awareness of MSCs

Out of 1895 contacted clinicians, 253 responded either positively or negatively to the invitation to take part in the survey (Fig. 1). Of the 148 clinicians who agreed to participate, 146 met the selection criteria and were included in

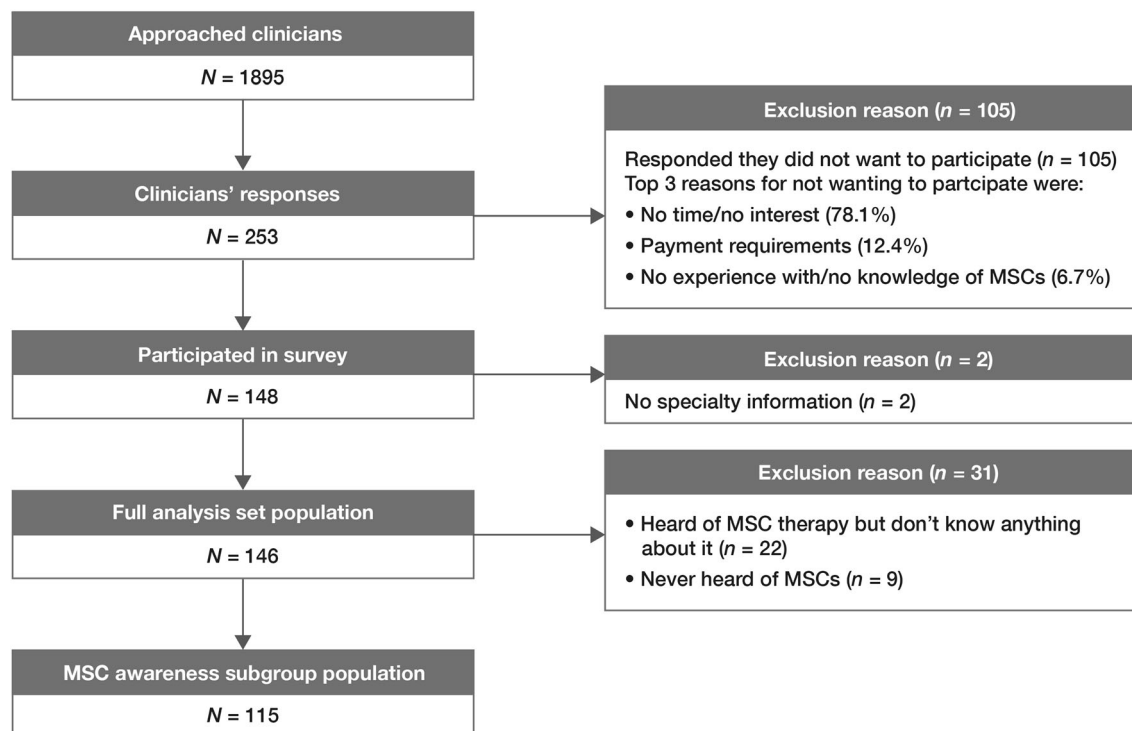


Fig. 1 Study population accrual. Clinicians were from Australia, Austria, Canada, Denmark, France, Germany, Israel, Italy, Japan, Netherlands, South Korea, Spain, Switzerland, UK, USA

the full analysis set (Fig. 1). Of these, only nine (6.2%; CI 2.9–11.4) reported that they never heard of MSCs and 22 (15.1%; CI 9.7–21.9) that they heard of this therapy but did not know anything about it. The remaining 115 (78.8%; CI 71.2–85.1) reported having limited, moderate, or strong awareness and were included in the MSCs awareness subgroup.

The level of awareness for the participating clinicians is shown in Fig. 2.

Clinicians' Characteristics

The characteristics and clinical experience of clinicians within the full analysis set and the MSC awareness subgroup are presented in Table 2. No relevant differences were observed between the two groups in terms of region and specialty (gastroenterologists and colorectal surgeons).

Experience with, Interest in, and Willingness to Use MSCs

Within the MSC awareness subgroup (i.e., clinicians with limited, moderate, or strong awareness of MSCs), only 21 (21/112, 18.8%; CI 12.0–27.2) reported having treated patients suffering from refractory perianal fistulizing Crohn's disease with MSCs, with a median of four treated patients per clinician up to the time of the survey (minimum 1, maximum 30). Within the full analysis set (i.e., all clinicians meeting the inclusion criteria, $N = 146$), this corresponds to 14.4%.

Despite limited experience treating patients with MSCs in clinical practice, the vast majority of the MSC awareness subgroup reported having large or moderate interest (98/113, 86.7%; CI 79.1–92.4) in MSCs and over half of them stated they kept themselves regularly up to date with developments in this therapeutic field (58/109, 53.2%; CI 43.4–62.8). In addition, the majority (89/108, 82.4%; CI 73.9–89.1) reported

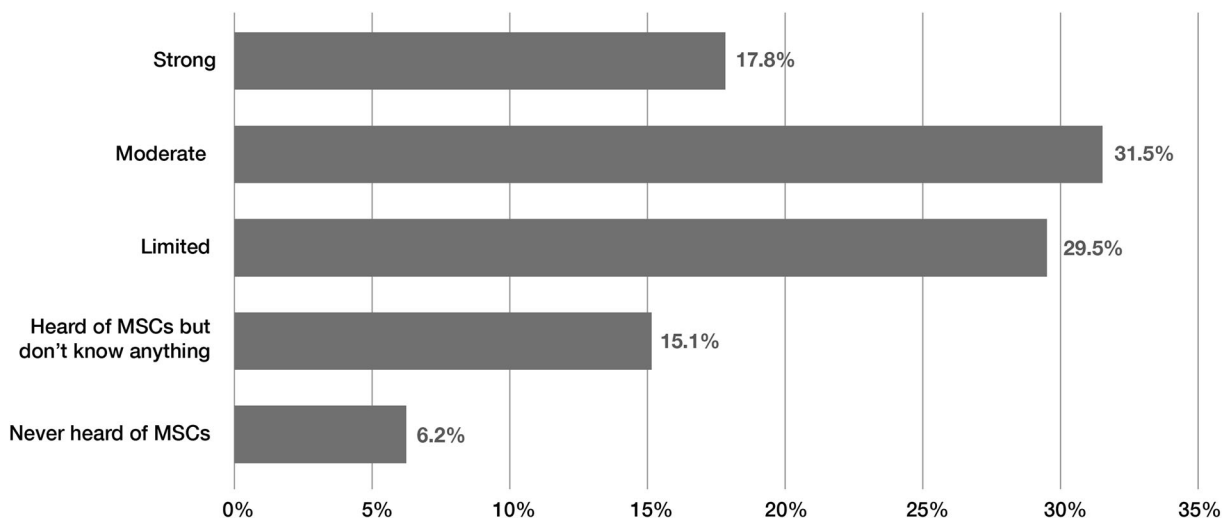


Fig. 2 Level of awareness of MSCs within the full analysis set. The full analysis set included all clinicians agreeing to take part in the survey and meeting the selection criteria ($N = 146$). MSC mesenchymal stem/stromal cell

willingness to use MSCs in the fistulizing Crohn's disease indication. Reasons for being willing or not willing to use MSCs in this indication were provided using the free-text fields. Willingness to use was mainly related to failure of previous treatments (e.g., "limited therapy options," "deficiency of other available therapies," "failure with previous treatments," "to avoid surgery"), complex patient profiles (e.g., "refractory," "difficult to treat," "severe," "young"), acknowledgement of positive efficacy and safety of MSCs ("a lot of success," "very safe if the patient is willing," "easy administration procedure"), or prior experience with using this therapy (e.g., "already participate in darvadstrocel application," "experience in other stem cell trials," "we have the accreditation," "we are one of two centers in the country using darvadstrocel"). Unwillingness to use, reported by 19 clinicians (19/108, 17.6%; CI 10.9–26.1), was mainly related to insufficient knowledge, evidence, or experience (e.g., "not enough knowledge yet to know efficacy and safety," "no sufficient safety data in Japan," "lack of experience currently"), and institution regulations and logistics (e.g., "I have not enough patients to include and the logistics seems to be heavy," "do not have the infrastructure to support this service at this time," "organization for MSCs is

not constructed"). One clinician indicated unwillingness due to being "not interested" and one clinician indicated unwillingness due to using "standard therapy first." Notably, none of the clinicians reported not being willing to use MSCs due to unfavorable efficacy or safety of this therapy.

Clinicians' Self-Perceived and Objective Knowledge of MSCs

On the basis of their self-perception, the proportion of clinicians who reported having limited or no knowledge of MSCs in general and of their safety, efficacy, mechanism of action, and preparation or delivery process in the perianal fistulizing Crohn's disease indication ranged between 50.5% (53/105; CI 40.5–60.4) and 64.8% (68/105; CI 54.8–73.8) (Fig. 3). Similarly, just over a third stated having familiar or expert knowledge in general (38/105, 36.2%; CI 27.0–46.1) and of the mechanism of action in the targeted indication (37/105, 35.2%; CI 26.2–45.2). In the full analysis set, this corresponds to 26.0% and 25.3%, respectively.

Regarding objective knowledge questions, perianal fistulizing Crohn's disease (69/106, 65.1%; CI 55.2–74.1) and GvHD (17/106,

Table 2 Clinicians' characteristics and clinical experience

	Full analysis set (total = 146)	MSC awareness subgroup (total = 115)
Medical specialty		
Number of respondents, <i>N</i> (% of total)	146 (100)	115 (100)
Gastroenterologist, <i>n</i> (% of <i>N</i>)	128 (87.7)	101 (87.8)
Colorectal surgeon, <i>n</i> (% of <i>N</i>)	18 (12.3)	14 (12.2)
Geographic region		
Number of respondents, <i>N</i> (% of total)	146 (100)	115 (100)
Europe, <i>n</i> (% of <i>N</i>)	78 (53.4)	68 (59.1)
Americas, <i>n</i> (% of <i>N</i>)	28 (19.2)	16 (13.9)
Rest of the world, <i>n</i> (% of <i>N</i>)	40 (27.4)	31 (27.0)
Age (years)		
Number of respondents, <i>N</i> (% of total)	138 (100)	112 (100)
25–34 years	3 (2.2)	2 (1.8)
35–44 years	35 (25.4)	25 (22.3)
45–54 years	47 (34.1)	40 (35.7)
55+ years	53 (38.4)	45 (40.2)
Number of years practicing		
Number of respondents, <i>N</i> (% of total)	137 (100)	112 (100)
< 5 years, <i>n</i> (% of <i>N</i>)	3 (2.2)	2 (1.8)
5–10 years, <i>n</i> (% of <i>N</i>)	12 (8.8)	8 (7.1)
> 10 years, <i>n</i> (% of <i>N</i>)	122 (89.1)	102 (91.1)
Type of institution		
Number of respondents, <i>N</i> (% of total)	146 (100)	115 (100)
District general hospital, <i>n</i> (% of <i>N</i>)	22 (15.1)	16 (13.9)
Academic hospital, <i>n</i> (% of <i>N</i>)	93 (63.7)	83 (72.2)
Private practice, <i>n</i> (% of <i>N</i>)	23 (15.8)	11 (9.6)
Research laboratory, <i>n</i> (% of <i>N</i>)	1 (0.7)	1 (0.9)
Other, <i>n</i> (% of <i>N</i>)	7 (4.8)	4 (3.5)
Patients with inflammatory bowel disease seen per month		
Number of respondents, <i>N</i> (% of total)	132 (100)	110 (100)
Mean (SD)	91.2 (113.7)	101.8 (119.9)
Median (P25, P75)	50 (15.0, 120.0)	60 (20.0, 120.0)
Min–max patients per clinician ^a	0.0–600.0	0.0–120.0

Table 2 continued

	Full analysis set (total = 146)	MSC awareness subgroup (total = 115)
Number of patients with Crohn’s disease seen per month		
Number of respondents, <i>N</i> (% of total)	130 (100)	109 (100)
Mean (SD)	43.1 (53.4)	48.7 (56.4)
Median (P25, P75)	20 (10.0, 50.0)	30 (10.0, 60.0)
Min–max patients per clinician ^a	0.0–300.0	0.0–300.0
Number of patients with perianal fistulizing Crohn’s disease seen per year		
Number of respondents, <i>N</i> (% of total)	130 (100)	109 (100)
Mean (SD)	24.1 (39.8)	27.5 (42.5)
Median (P25, P75)	10 (5.0, 30.0)	10 (5.0, 30.0)
Min–max patients per clinician ^a	0.0–250.0	0.0–250.0
Attendance of any of the following in the past 2 years		
Number of respondents, <i>N</i> (% of total)	135 (100)	110 (100)
Gastroenterology/colorectal surgery conferences, <i>n</i> (% of <i>N</i>)	130 (96.3)	108 (98.2)
Number of respondents, <i>N</i> (% of total)	136 (100)	112 (100)
Discussion or presentation on MSC therapy, <i>n</i> (% of <i>N</i>)	83 (61.0)	81 (72.3)

The full analysis set included all clinicians agreeing to take part in the survey and meeting all the selection criteria (*N* = 146). The MSC awareness subgroup included clinicians reporting limited, moderate, or strong awareness of MSCs (*N* = 115)

MSC mesenchymal stem/stromal cell, P25/75 25th/75th percentile, SD standard deviation

^aThis was an open question with no suggested range options. Therefore, this data is to be interpreted with caution as it may be susceptible to errors in responding (e.g., clinicians in large practice centers reporting the number of patients at the center rather than patients they personally see). To limit this potential bias, study interpretations are based on the non-parametric statistics that are less affected by single data point anomalies

16.0%; CI 9.6–24.4) were the indications most commonly reported as being approved for treatment with MSCs in the USA, Europe, or Japan. In addition, five clinicians (5/106, 4.7%; CI 1.5–10.7) reported “other” and specified in the free-text the following indications: blood disorders, pancreatitis, COVID-19, multiple sclerosis, systemic sclerosis, severe burn injury, and ophthalmology disease. Lastly, a substantial proportion (25/106, 23.6%; CI 15.9–32.8) reported not knowing which indication MSCs are approved for.

Clinicians’ responses concerning terms that best describe MSCs in general and their mechanism of action in the targeted indication are shown in Fig. 4. The terms “immunomodulatory therapy” (Fig. 4a) and “immunomodulation” (Fig. 4b), considered to be the most appropriate terms among the options provided in this study, were chosen by only 33.7% (35/104; CI 24.7–43.6) and 36.2% (38/105, CI 27.0–46.1) of the clinicians. This corresponds to 24.0% and 26.0% within the full analysis set.

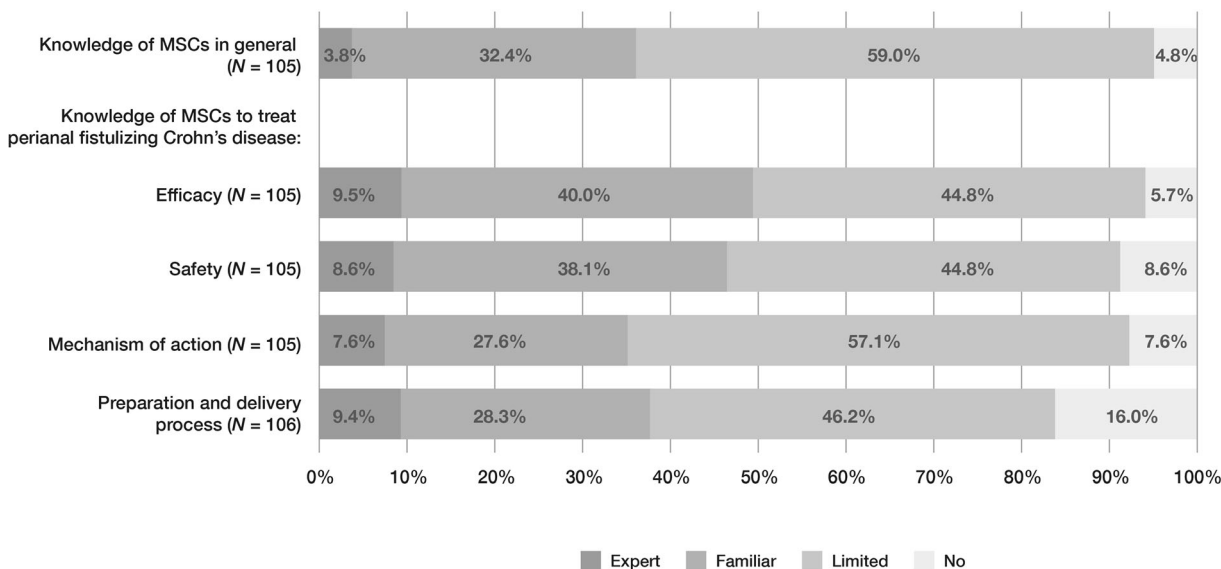


Fig. 3 Self-perceived knowledge within the MSCs awareness subgroup. The MSC awareness subgroup included clinicians reporting limited, moderate, or strong awareness of MSCs ($N = 115$). *MSCs* mesenchymal stem/stromal cells

Clinicians' Perception of MSCs

The vast majority of the MSC awareness subgroup (94/101, 93.1%; CI 86.2–97.2) believed that MSCs can address an unmet need for patients with perianal fistulizing Crohn's disease. This corresponds to 64.4% of the full analysis set ($N = 146$). Reasons reported in the free-text mainly related to an unmet need for patients when the standard therapy failed (e.g., "failure to respond to standard therapy," "refractory patients"), and also to when no effective therapy exists (e.g., "a group of patients with no valid treatment alternative," "difficult to treat," "patients that are without an effective treatment now," "patients with poor quality of life"). Among the clinicians who reported that MSC therapy does not address an unmet need (7/101, 6.9%; CI 2.8–13.8), four indicated reasons using the free-text explanation question. Of these, three clinicians addressed their lack of knowledge or insufficient evidence ("lack of knowledge from my side," "have not heard about MSC efficacy in this regard," "there are no sufficient safety data in my country") and one clinician stated that "the cause of disease

remains untreated, this is only a symptomatic therapy." A substantial proportion of the MSC awareness subgroup (49/107, 45.8%; CI 36.1–55.7) also expressed concerns about using this therapy in the targeted indication. The types of concerns detailed by 47 of these clinicians are shown in Fig. 5.

The preferred sources of information to alleviate concerns were colleagues (peers or clinicians) with experience in the field, medical and scientific associations, industry manufacturers, and regulators (Fig. S1 in the ESM). The preferred types of information were published data from clinical trials, real-world studies, and conference or congress presentations (Fig. S2 in the ESM). These were also the three main types of information that provided reassurance to the clinicians who stated having no concerns about using MSCs in the fistulizing Crohn's disease indication (Fig. S3 in the ESM).

Analysis by Medical Specialty and Type of Institution

Of the 115 clinicians in the MSCs awareness subgroup, 101 were gastroenterologists (101/

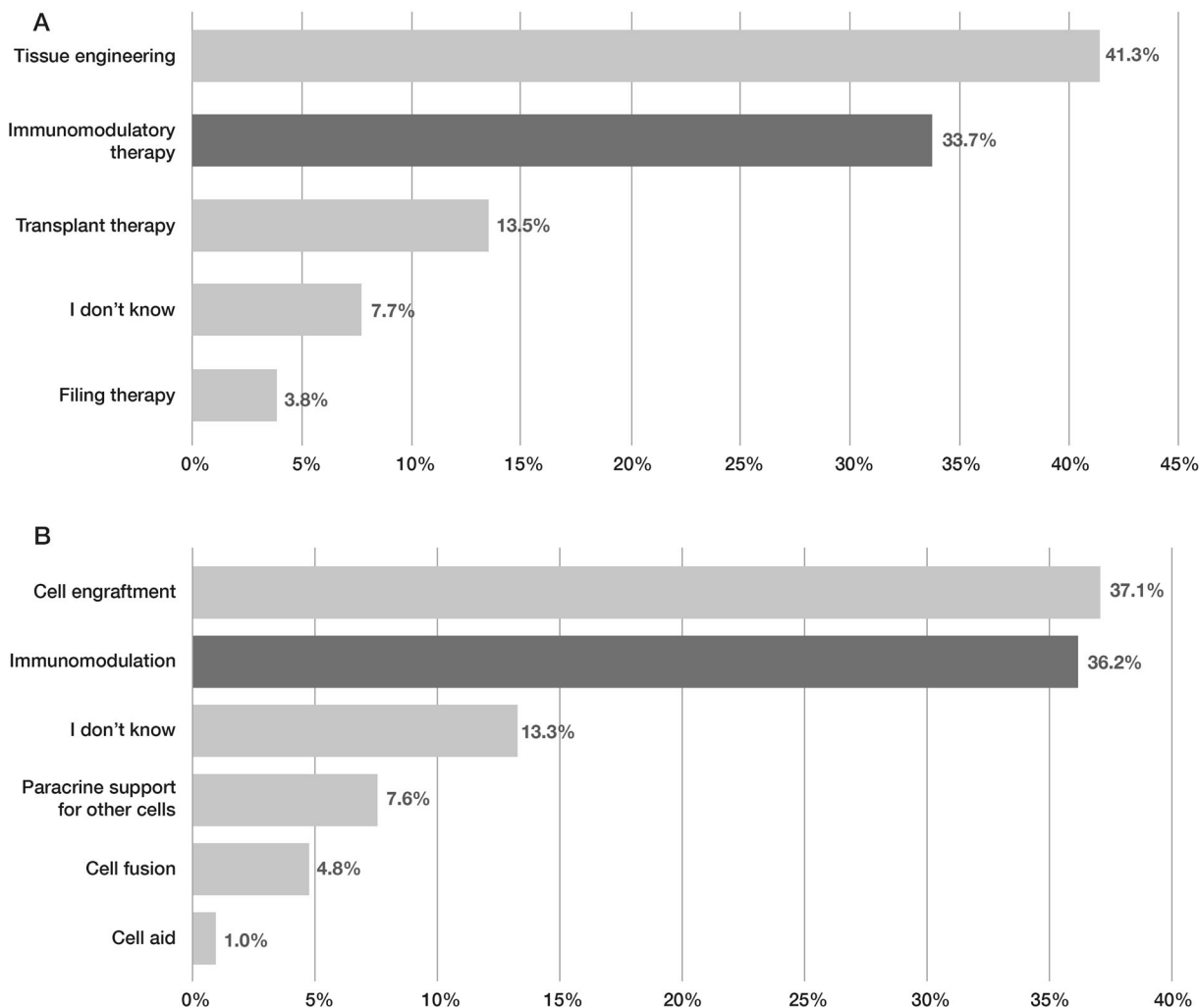


Fig. 4 Objective knowledge among clinicians within the MSC awareness subgroup: **a** term that best describes MSC therapy ($N = 104$); **b** term that best describes the mechanism of action of MSCs for patients with perianal fistulizing Crohn’s disease ($N = 105$). The MSC

awareness subgroup was defined as clinicians reporting limited, moderate, or strong awareness of MSCs ($N = 115$). Dark gray bars indicate the choices considered by authors as the most appropriate responses among the options provided. *MSCs* mesenchymal stem/stromal cells

115, 87.8%) and 14 were colorectal surgeons (14/115, 12.2%). In addition, the vast majority (83/115, 72.2%) were working for an academic hospital, while a smaller proportion were working for a district general hospital or other types of institutions (16/115, 13.9% in both groups). The results by medical specialty and type of institution are described in Tables S1 and S2 in the ESM. Despite the small sample size, it is interesting to note that more colorectal surgeons than gastroenterologists reported having moderate or strong awareness of MSCs

(92.9% vs 58.4%), moderate or large interest in this therapy (100% vs 84.8%), familiar or expert knowledge of it (64.3% vs 31.9%), and willingness to use it in clinical practice (100% vs 79.8%).

Factors Associated with Increased Awareness of MSCs

Through univariable logistic regression, marginal associations or trends were observed

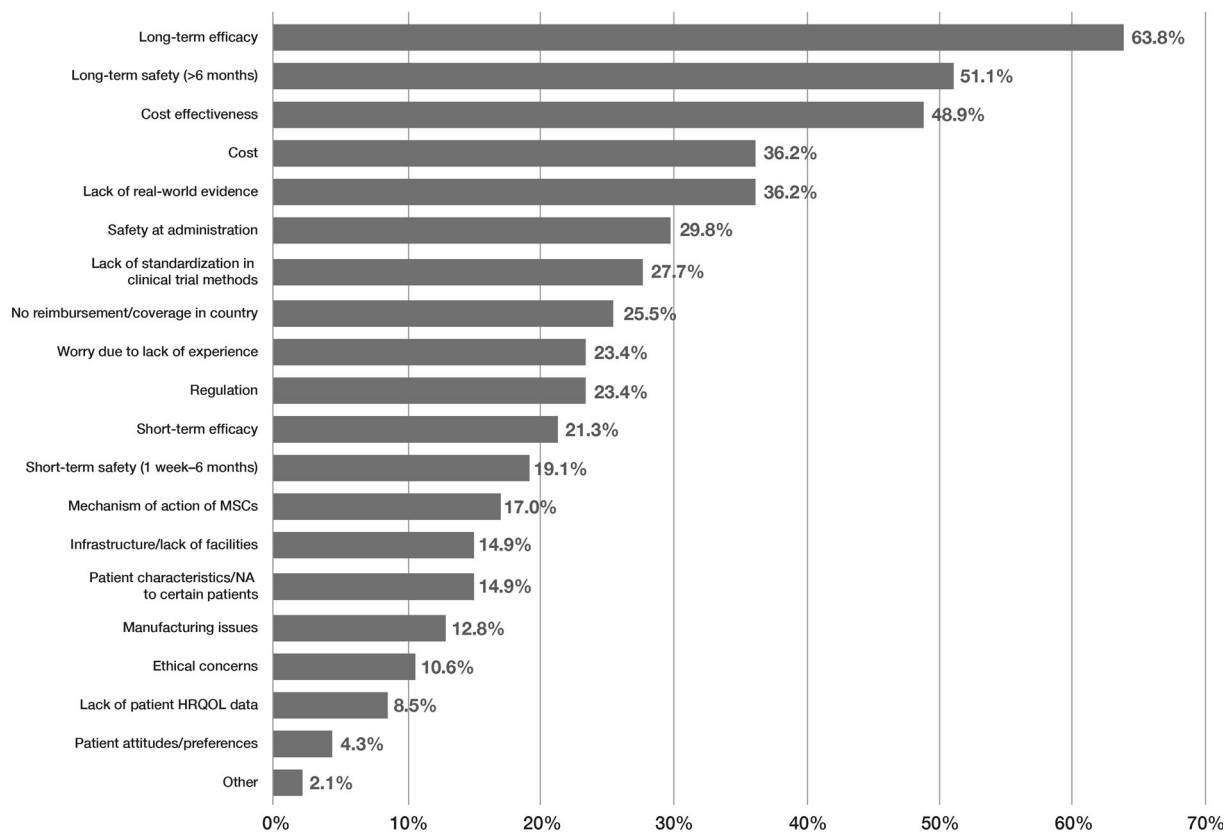


Fig. 5 Types of concerns using MSCs in the perianal fistulizing Crohn's disease indication. Responses provided by 47 of the 49 clinicians who stated having concerns using this therapy. *MSCs* mesenchymal stem/stromal cells

between all the tested factors and the likelihood of reporting strong or moderate MSC awareness (Table S3 in the ESM). After adjustment in the multivariable logistic regression model, clinicians who attended any discussions or presentations on MSCs in the last 2 years (odds ratio [OR] 18.64; CI 4.59–75.74; $P < 0.05$) and those seeing a higher number of patients with perianal fistulizing Crohn's disease per year (OR 1.08; CI 1.04–1.12; $P < 0.05$) were significantly more likely to report strong or moderate awareness (Table 3).

DISCUSSION

Despite growing and robust evidence existing on the safety and efficacy of MSCs in different disease areas, including fistulizing Crohn's disease [3, 9], the application of this novel therapy

in clinical practice is lagging behind. Thus, we conducted an international survey in 15 different countries to investigate the awareness, current knowledge, and perspectives of MSCs among gastroenterologists and colorectal surgeons who may be using or considering using this therapy to treat their patients. The results show that the vast majority of the surveyed clinicians are interested in and willing to use MSCs and believe that this therapy addresses unmet needs for patients with perianal fistulizing Crohn's disease. However, less than one-fifth reported having ever treated a patient with MSCs and the majority showed knowledge gaps about this therapy and its mechanism of action, even though almost all the clinicians were experienced specialists with over 10 years of practice. This could be explained by the higher costs of MSCs compared to other existing therapies, as financial restrictions may hamper their

Table 3 Multivariable logistic regression for associations between clinicians’ characteristics and level of awareness of MSCs

	OR	CI	P value
Geographic region vs Europe ^a			0.3150 ^b
Americas	0.28	0.04–1.74	0.1713
Rest of world	1.08	0.28–4.17	0.9163
Institution type vs academic hospital ^a			0.2715 ^b
District general hospital	0.32	0.08–1.35	0.1225
Other	1.17	0.25–5.33	0.8437
Medical specialty vs gastroenterologists ^a			
Colorectal surgeons	2.04	0.48–8.68	0.3357
Number of years practicing vs ≤ 10 years ^a			0.1862 ^b
11–20 years	2.27	0.31–16.34	0.4172
> 20 years	4.95	0.70–34.92	0.1083
Attendance at discussion/presentation on MSCs in last 2 years vs no ^a	18.64	4.59–75.74	< 0.0001
Increasing number of patients with perianal fistulizing Crohn’s disease seen per year ^a	1.08	1.04–1.12	0.0002

Multivariable logistic regression performed among clinicians within the full analysis set who had no missing responses (*N* = 130). The full analysis set included all clinicians agreeing to take part to the survey and meeting all the selection criteria

CI 95% confidence interval, MSCs mesenchymal stem/stromal cells, OR odds ratio

^aObservations with missing responses are not included

^bWald chi-square test and associated *P* value indicate significance of overall variable to model

use, which in turn impedes knowledge and experience. Despite some clinicians stating that they were not using MSCs because of institution regulations and logistics, almost half of them expressed concerns about using this therapy in routine practice, suggesting that they may have a negative perception or limited knowledge of the efficacy, safety, and applicability of MSCs in mainstream healthcare.

It is important to note that almost 80% of the surveyed clinicians had at least some level of awareness of MSCs and almost 90% were interested in this novel therapy. In addition, almost 80% of the gastroenterologists and all of the colorectal surgeons were willing to use MSCs to treat perianal fistulizing Crohn’s disease. Our results reflect the enthusiasm among the scientific community for this promising therapy in general and for its application in the approved indication. Notwithstanding, more than half of the clinicians felt they have no or limited

knowledge of it. This was also reflected by the observed high heterogeneity as to the assumed definition of MSCs in general and their mechanism of action when applied to perianal fistulizing Crohn’s disease, with the most prevalent answer choices being “tissue engineering” and “cell engraftment.” This uncertainty might be due to the large variety and still not fully understood mechanisms involved in the therapeutic effects of MSCs across different disease areas and clinical applications [1, 15]. However, animal and clinical studies over the past few years have provided additional clarity around the mechanism of action of this therapy. It is now well accepted that MSCs do not engraft in the tissue of the host and that instead they orchestrate local and systemic innate and adaptive immune responses through the release of an array of bioactive mediators, especially when exposed to an inflammatory environment, such as that of Crohn’s disease or GvHD

[1, 20, 21]. Therefore, MSCs can be described as an immunomodulatory therapy. The suboptimal knowledge responses along with the self-perceived knowledge deficit observed in this study suggest a need for further education for clinicians in this field. Although results by specialty group should be interpreted with caution because of the small sample size, the fact that there was more uncertainty among gastroenterologists than colorectal surgeons seems to indicate that there is a special need to further educate gastroenterologists to facilitate their ability to convey information adequately to patients when considering treatment with MSCs as an alternative to more invasive surgeries.

Many clinical trials have demonstrated that MSCs can be a valid treatment option in otherwise difficult-to-treat disorders such as GvHD, fistulizing Crohn's disease, and others [4, 9]. In line with these findings, irrespective of their medical specialty or the institution of practice, almost all clinicians reported that MSCs address an unmet need for patients with perianal fistulizing Crohn's disease, suggesting that even clinicians with limited awareness or knowledge had a belief in the potential of this novel therapy in this indication. However, almost half of the clinicians with at least limited awareness reported having concerns about using this therapy to treat perianal fistulizing Crohn's disease. Although only a small number of clinicians detailed their concerns ($N = 47$), the results suggest the main issues were related to long-term efficacy or safety and economic issues (cost or cost-effectiveness). On the basis of these data alone, it was not possible to determine whether the reported concerns relate to perceived inadequacy of MSCs or lack of knowledge or understanding. Indeed, the efficacy of MSCs in some disease areas is still under debate [15, 22]. It has been reported that the diversity of MSC sources, their different clinical applications, and the many aspects of their mechanism of action that have not yet been thoroughly investigated are sources of debate and controversy about the therapeutic application of these cells [2]. This evidence likely generates hesitancy in using MSCs in routine practice. However, when considering clinicians'

verbatim free-text responses, no clinician who reported that they would not be willing to use this therapy in clinical practice indicated inadequacy of treatment. Therefore, our study suggests concerns were most likely related to a lack of knowledge and understanding. Interestingly, irrespective of whether clinicians had current concerns, the most common types of information requested to alleviate concerns were published data from clinical trials or real-world studies and conference or congress presentations. Taken together, these results suggest that wider dissemination of scientific results and targeted medical education strategies, especially in the approved indications such as perianal fistulizing Crohn's disease, should help alleviate clinicians' concerns around MSCs.

Although our study was not designed to infer causality and despite potential biases that may have occurred as a result of the combination of small sample size and low number of outcome events (strong or moderate awareness), the results of the logistic regression suggest that clinicians who had attended any discussion or presentation on MSCs in the last 2 years were much more likely to report strong or moderate awareness. In addition, for each additional patient with perianal fistulizing Crohn's disease seen per year, the likelihood of reporting strong or moderate awareness of MSCs increased. These results fit within the aforementioned findings that while clinicians seem to be keen on identifying new treatment options to target patients' unmet needs, effective communication concerning MSCs is likely to have a positive effect on their awareness of this novel therapy.

This study has several strengths. It was conducted in 15 different countries, thus providing a picture of the attitudes of clinicians across the world. The protocol was approved by an independent research board and the study was conducted according to the approved protocol. Among the participants, completeness of the questionnaire was high, with only a few missing responses throughout, and many clinicians also provided insightful information through free-text responses. However, this study also has some limitations that should be considered when interpreting the results. First, the

response rate to the invitation to participate in the survey was only 13% (253/1895). This value is similar to that reported in a survey involving gastroenterologists and colorectal surgeons in the Netherlands (8–14%) [23], but it is on average lower than that reported in other surveys about stem cells (39–57%) [24, 25] or involving gastroenterologists and surgeons in other countries (22–44%) [26–28]. The lower response rate of this study may be because clinicians did not receive compensation for completing the questionnaire. In addition, the recruitment for this survey was carried out in 2020, during the still-ongoing global pandemic of COVID-19. In this situation, clinicians may have had less time to involve themselves in scientific activities around MSCs. Second, the small sample size has reduced the generalizability of the results in some subgroups (e.g., colorectal surgeons, clinicians working in district general hospitals as opposed to academic hospitals, and some of the selected countries), as well as the power of the logistic regression to detect associations. Third, clinicians with a lack of knowledge or interest in MSCs were less likely to participate in the survey, suggesting that proportions in the full study population (full analysis set) may be overestimated as a result of lack of representativeness. Finally, as a result of local hospital regulation changes related to the COVID-19 pandemic, it is likely that clinicians may have seen fewer patients per month; thus, this data may be underestimated in our sample.

CONCLUSIONS

Our findings indicate that among the participating gastroenterologists and colorectal surgeons who reported having some awareness of MSCs, there is large interest in this novel therapy and willingness to use it in routine practice, as they believe MSCs can address unmet needs for their patients. Nonetheless, there is an urgent need to increase their knowledge of what MSCs are and how they work to alleviate existing concerns. Therefore, further communication and education solutions are needed to support clinicians in their decision-making and to foster adoption of MSCs to treat patients with

perianal fistulizing Crohn's disease. By identifying the preferred sources of information and the key areas of concerns, the present results can be used to inform the development of targeted education strategies.

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Compliance with Ethics Guidelines. This study was approved by the New England Institutional Review Board (protocol number Alofisel-5006, 10 April 2020).

Data Availability. All data relevant to the study are included in the article or in the Online Resources.

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