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Prevalence of anti-TNF contraindications in Crohn's disease: A cross-sectional survey from the GETAID

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Title: Prevalence of anti-TNF contraindications in Crohn's disease: a cross-sectional survey from the GETAID

Short title: Anti-TNF contraindications and IBD specialists

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19 *The data underlying this article will be shared on reasonable request to the corresponding*
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28 **All the members of the GETAID-patient experience study group are listed in the**
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Stéphane Nahon reported a relationship with Janssen, Pfizer, Takeda, MSD, Gilead, Ferring

Marion Simon reported a relationship with Abbvie, Mylan, Takeda and Amgen

Lucas Guillo has received lecture and consulting fees from Abbvie

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SUMMARY

Background: The exact rate of contraindications to anti-TNF therapy and physician perspectives on treatment choices facing to anti-TNF contraindication, are poorly reported.

Methods: A two-week cross-sectional study was conducted in 31 centres. Physicians completed a questionnaire for a total of 1,314 consecutive outpatients with Crohn's disease, assessing each patient's potential contraindications to anti-TNF therapy, the choice of alternative therapy to anti-TNFs, and their preference in an unrestricted reimbursement setting.

Results: Among the 1,293 responses to the first item, 148 (11.5%) reported 32 absolute contraindications (2.5%) and 116 relative contraindications (9.0%) to anti-TNF therapy. When asked about their preference of alternative therapies in those cases with contraindications to anti-TNF, physicians chose ustekinumab and vedolizumab, 75.6% and 23.9%, respectively. In multivariable analysis, the choice of vedolizumab was the preferred choice for patients aged > 60 years with the L2 phenotype and the absence of perianal lesions. In a hypothetical setting of unrestricted reimbursement, anti-TNFs remained physicians' preferred first-line biological therapy choice for 78.2%.

Conclusion: Anti-TNF contraindications occurred in up to 11.5% of patients with Crohn's disease. Physicians' choices for alternative therapy to anti-TNF relied on ustekinumab in 75.6% and vedolizumab in 23.9% of these cases. This choice was driven mainly by phenotypical criteria and age.

INTRODUCTION

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3 Inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis,
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5 are chronic, disabling diseases affecting the gastrointestinal tract[1,2]. The epidemiology of
6
7 IBD is characterized by an increasing incidence and prevalence, occurring in close relation to
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9 the acquisition of Western lifestyles[3]. The rising incidence across all age groups together with
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11 the ageing of the general population has resulted in a continuous increase in the prevalence of
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13 IBD among the elderly, along with associated comorbidities[4].
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18 The proportion of patients with Crohn's disease treated with biological agents is
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20 growing due to their efficacy and earlier use in preventing bowel damage[5]. According to the
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22 French national health insurance database, the probabilities of being treated with anti-TNF
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24 monotherapy and combination therapy were 34% and 18% in patients with Crohn's disease,
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26 respectively[6]. Such a paradigm may lead to an increased risk of drug class-specific
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28 complications, infections and malignancies, especially among the elderly[7].
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33 The risk of treatment-related complications can be lowered by respecting specific
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35 contraindications to a drug. The principal contraindications to anti-TNF therapy have been
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37 described in the London Position Statement of Biological Therapy and include active infection,
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39 untreated latent tuberculosis, known hypersensitivity to the agent, pre-existing demyelinating
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41 disease or optic neuritis, current malignancy, history of lymphoma, previous malignancy with
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43 significant risk of recurrence and severe congestive cardiac failure[8]. It should be noted that
44
45 many of the latter contraindications to anti-TNF therapy may be transient and/or relative and
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47 could be overcome with time and/or with a specific monitoring protocol. In a retrospective
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49 cohort study of adult patients with moderate-severe Crohn's disease, 25.6% were excluded from
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51 anti-TNF randomized controlled studies because of comorbid conditions such as poorly
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53 controlled cardiovascular or pulmonary disease and malignancies[9]. However, real-world
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55 management often differs from that of randomized controlled trials. In addition, new therapeutic
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1 classes that may be safer than earlier classes may be an alternative to first-line anti-TNF
2 therapies.
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5 Therefore, the aim of the present study was to assess the prevalence of anti-TNF
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7 contraindications in a large multicentre cross-sectional cohort study of patients with CD and to
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9 assess IBD specialists' preferences and underlying determinants of their treatment choices in
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11 cases with anti-TNF contraindications.
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PATIENTS AND METHODS

Study population

This was a cross-sectional survey including all consecutive adult outpatients with CD seen during two consecutive weeks in September 2020. Physicians belonged to 31 tertiary centres in France affiliated with the Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif (GETAID). The study was conducted in accordance with the ethical principles and French regulatory agency requirements. Questionnaires aimed to assess determinants of prescription of physicians and not patients. Each questionnaire was therefore filled out by physicians alone. For such study, patients' information and ethical committee submission were not mandatory.

Survey instrument

For each patient, a 2-page self-administered questionnaire was designed by the Educational GETAID Committee and then submitted to 5 physicians to assess the reliability of the questionnaire (supplementary material, Figure S1). The final questionnaire was designed to explore the following:

- Patients and Crohn's disease characteristics, including demographics, type of Crohn's disease according to Montreal classification, duration of Crohn's disease, age at diagnosis of Crohn's disease, history of intestinal surgery and/or surgery for Crohn's disease.
- Treatment history and current treatment of Crohn's disease.
- Presence of an absolute or relative contraindication to anti-TNF therapy and, if present, the reason for the contraindication. Absolute contraindication was defined as a situation which makes the use of anti-TNF absolutely inadvisable. Relative contraindication was defined as a condition when anti-TNF should be used with particular caution

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- Assuming the patient has a relative contraindication to anti-TNF therapy and needs to be treated or switched to another biological therapy, then what treatment would you choose? Vedolizumab, ustekinumab or tofacitinib?

- Assuming that your patient is naïve to any biological therapy, what treatment would you choose as a first-line biological therapy in the setting of unrestricted reimbursement: Intravenous anti-TNF, subcutaneous anti-TNF i.e. adalimumab, vedolizumab, ustekinumab or tofacitinib?

Tofacitinib was proposed as first-line biological therapy whereas it is not recommended for patients with Crohn's disease. This is related to compassionate use of tofacitinib in some patients with refractory Crohn's disease with no other treatment opportunity.

The questionnaire was completed by a physician and retrieved after completion. We also collected the characteristics of each investigator (n=26), including age, gender, years of experience as senior gastroenterologist, number of weekly appointments with patients with CD, decision-making process before starting a biologic agent, daily practice therapeutic goals and major properties of a biological agent according to the physician's understanding (efficacy, safety, cost, mode of action, mode of administration).

Study outcomes

Study outcomes included the rate of absolute and relative contraindications to anti-TNFs, the best choice of biological agents in patients with relative contraindications to anti-TNFs, and the best retrospective choice for first-line biological therapy in Crohn's disease according to contraindications to anti-TNFs and patient characteristics.

Statistical analysis

The data were expressed as numbers (%) for qualitative data and as the mean \pm standard deviation (SD) or median [interquartile range] for quantitative data. To identify predictors of choice of a biological agent (vedolizumab or ustekinumab), univariate analysis using the Chi²

1 test was performed. Subsequent multivariate analysis using binary logistic regression models
2 was performed and adjusted for use of the abovementioned variables. Variables with $p < 0.10$
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4 in the univariate analysis were considered potential adjustment variables for the multivariate
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6 analysis. Quantitative values were converted into qualitative values by dichotomy with the
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8 median value. All the analyses were two-tailed, and p values less than 0.05 were considered
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10 significant. All statistics were calculated using SPSS Statistics v23® software (IBM Corp,
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12 Armonk, NY, USA).
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16 17 **RESULTS**

18 19 **Study population**

20 We included 1,314 patients with Crohn's disease from 31 tertiary centres (23 university
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22 hospitals and 8 general hospitals) in the present study (median age of 40.0 [30.0-52.0] years,
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24 47.3% male and a median Crohn's disease duration of 12.3 [6.3-20.3] years). Table 1
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26 summarizes the main characteristics of the study population. Current treatment included 5-
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28 aminosalicylates in 2.5% of the cases, immunomodulators alone in 4.5%, anti-TNF agents in
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30 58.9%, ustekinumab in 11.3%, vedolizumab in 6.6% and tofacitinib in 0.6%. No treatment was
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32 currently prescribed in 14.8% of the cases.
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40 41 **Anti-TNF contraindications**

42 Among the 1,293 respondents, 148 (11.5%) reported absolute and relative
43
44 contraindications to anti-TNF (Figure 1). Absolute contraindications were noted in 32 (2.5%)
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46 patients, and of those, eight (25.0%) were related to multiple sclerosis, six (18.75%) to chronic
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48 cardiac failure, six (18.75%) to concomitant neoplasia, six (18.75%) to infectious risk and six
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50 (18.75%) to history of anti-TNF adverse events. Relative contraindications were noted in 116
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52 (9.0%) patients, and of those, 43 (37.1%) were related to a history of neoplasia, 36 (31.0%) to
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2 a risk of infection, 21 (18.1%) to miscellaneous comorbidities, 9 (7.8%) to a history of anti-
3 TNF adverse events and 7 (6.0%) to systemic lupus erythematosus.
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5 When we asked for physician preferences in cases of contraindications to anti-TNFs and
6 the need to either treat the patient or switch the patient to another biological therapy, the
7 physicians' choice of ustekinumab was noted in 75.6% of cases, whereas the choices of
8 vedolizumab and tofacitinib were noted in 23.9% and 0.5% of cases, respectively.
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10 **Predictor of vedolizumab as the best choice in cases of contraindication to anti-TNF** 11 **therapy** 12 13 14 15

16 In univariate analysis, the choice of vedolizumab as an alternative biological agent in
17 cases of contraindication to anti-TNFs was significantly higher among patients aged > 60 years,
18 L2 phenotype, B1 phenotype, CD duration > 10 years, and who underwent prior and current
19 vedolizumab therapy (Table 2). On the other hand, the choice of vedolizumab as an alternative
20 biological agent in cases of contraindication to anti-TNF therapy significantly decreased among
21 patients of male sex, L1 phenotype, B2 phenotype, perianal lesions, prior and current anti-TNF
22 and ustekinumab therapy.
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39 In the multivariate analysis stratified on current use of vedolizumab, the choice of
40 vedolizumab as an alternative biological agent in cases of contraindication to anti-TNFs was
41 significantly increased in patients aged > 60 years (HR = 1.91, 95%CI[1.06-3.45], p = 0.03)
42 and of the L2 phenotype (HR = 3.28, 95%CI[1.96-5.52], p < 0.001) and significantly decreased
43 among patients with perianal lesions (HR = 0.39, 95%CI[0.22-0.69], p = 0.001) (Table 2).
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52 **Predictor of ustekinumab as best choice in cases of contraindication to anti-TNF therapy** 53 54

55 In univariate analysis, choice of ustekinumab as an alternative biological agent in cases
56 of contraindication to anti-TNFs was significantly increased for male sex, L1 phenotype, B2
57 phenotype, perianal lesions, prior and current anti-TNF therapy and current ustekinumab
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1 therapy (Table 3). On the other hand, in univariate analysis, the choice of ustekinumab as an
2 alternative biological agent in cases with contraindication to anti-TNF therapy was significantly
3 decreased in patients aged > 60 years with the L2 phenotype, B1 phenotype, CD duration > 10
4 years, and prior and current vedolizumab therapy.
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10 In the multivariate analysis stratified on current use of ustekinumab, the choice of
11 ustekinumab as an alternative biological agents in cases with contraindications to anti-TNF was
12 significantly increased in patients with L1 phenotype (HR = 1.94, 95%CI[1.11-3.37], p = 0.02),
13 current use of infliximab (HR = 2.77, 95%CI[1.71-4.50], p < 0.001), and perianal lesions (HR
14 = 2.49, 95%CI[1.45-4.29], p = 0.001) and decreased in patients with L2 phenotype (HR = 0.32,
15 95%CI[0.18-0.55], p < 0.001) (Table 3).
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25 **Hypothetical preference for anti-TNF as first-line biological therapy assuming biological** 26 **naïve status and unrestricted reimbursement** 27

28 When we asked physicians to assume that patients were naïve to any biological therapy
29 and then to choose a treatment in the setting of unrestricted reimbursement, physicians chose
30 an anti-TNF therapy in 78.2% of cases (infliximab in 41.9%, adalimumab in 36.3%), and
31 ustekinumab in 13.9% and vedolizumab in 7.8% of cases.
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41 In univariate analysis, the choice of anti-TNF as hypothetical anti-TNF first-line therapy
42 was increased in patients with male sex, L2 phenotype, B3 phenotype, perianal lesions, prior or
43 current anti-TNF therapy. On the other hand, the choice of anti-TNF as hypothetical anti-TNF
44 first-line therapy was decreased in patients aged > 60 years, with any contraindication to anti-
45 TNFs, L1 phenotype, B1 phenotype, and prior or current vedolizumab and ustekinumab
46 therapy.
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56 In the multivariate analysis stratified on current use of vedolizumab and ustekinumab,
57 the choice of anti-TNF as a hypothetical first-line anti-TNF therapy was increased in patients
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with B3 phenotype (HR = 1.87, 95%CI[1.36-2.47], p = 0.009), perianal lesions (HR = 2.39, 95%CI[1.57-3.64], p < 0.001), and current anti-TNF therapy (HR = 2.39, 95%CI[1.53-3.03], p < 0.001) and decreased in patients aged > 60 years (HR = 0.45, 95%CI[0.29-0.71], p = 0.001) with any contraindication to anti-TNFs (HR = 0.35, 95%CI[0.22-0.56], p < 0.001).

DISCUSSION

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3 More than seven years after the approval of vedolizumab, anti-TNF therapy remains the
4 most frequently used first-line biological therapy in the treatment of Crohn's disease. In a recent
5 French nationwide cross-sectional study on 268,185 patients with IBD, anti-TNFs were more
6 than 5-times more frequently prescribed than vedolizumab and ustekinumab[10]. In our large
7 cross-sectional cohort study, we reported contraindications to anti-TNF therapy in up to 11.1%
8 of cases. In cases with contraindications to anti-TNF therapy, physicians were 3-times more
9 likely to prescribe ustekinumab than vedolizumab. When asked about their hypothetical first-
10 line biological therapy selections for biological treatment-naïve patients in the setting of
11 unrestricted reimbursement, physicians still prescribe anti-TNF therapy in 78.2% of cases.
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25 In France, the healthcare system requires anti-TNFs to be used as a first-line biological
26 therapy for both UC and CD, while vedolizumab and ustekinumab will be reimbursed only after
27 at least one anti-TNF has failed or in cases of contraindication to anti-TNFs. In a recent real-
28 world Italian survey of 100 physicians, patients with contraindications to anti-TNF therapy
29 accounted for 9% of patients, while another 11% of patients reported contraindications related
30 to previous anti-TNF therapy[11]. In the present study, both reasons for the use of anti-TNFs
31 despite contraindications were lower but remained significant. The major issue may be to
32 determine which contraindication is absolute and which contraindication can be overcome with
33 close monitoring. Only 2.5% of patients had absolute contraindications to anti-TNF therapies,
34 namely, those with congestive heart failure, demyelinating disease, known hypersensitivity to
35 anti-TNFs and recent neoplasia, for which anti-TNFs are prohibited by oncologists. For those
36 with relative contraindications that are more frequently seen, the use of anti-TNFs is
37 conditioned by the risk-benefit ratio for anti-TNFs and alternative biological agents.
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57 Neither vedolizumab nor ustekinumab share the same contraindications and safety
58 profiles as anti-TNFs. Indeed, network meta-analyses and population-based studies reported
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1 trends for better safety profiles that favour using both ustekinumab and vedolizumab rather than
2 anti-TNFs in cases with risk of infection and malignancy[12–15]. No head-to-head trial has
3 compared the efficacy of these two drugs in patients with Crohn’s disease. While indirect
4 comparison through network meta-analyses did not show any difference between vedolizumab
5 and ustekinumab, several cohort studies have indicated the superior effectiveness of
6 ustekinumab over vedolizumab in patients with Crohn’s disease[16–19]. However, a recent
7 study reported superiority of ustekinumab over vedolizumab in the short term but not in the
8 long term[16]. In the present study, physicians made the choice of ustekinumab in 75.6% of
9 patient cases with contraindications to anti-TNFs. This physician preference confirms the
10 importance of real-world experience that has yet to be supported by head-to-head trials.
11 Surprisingly, physicians remained very confident in prescribing anti-TNFs, possibly because of
12 the long history of this biologic; it is still prescribed as a first-line therapy in more than 75% of
13 cases.
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31 In terms of determinants of the choice between ustekinumab and vedolizumab in cases
32 of contraindications to anti-TNFs, differences in CD phenotype most influenced the physicians’
33 choice. On the one hand, vedolizumab was more frequently chosen in cases of purely colonic
34 disease and a non-stricturing, non-penetrating phenotype, whereas ustekinumab was more
35 frequently chosen in cases of purely ileal disease, a structuring phenotype and perianal lesions.
36 Whereas neither the location nor phenotype of CD has been reported to predict the efficacy of
37 either vedolizumab or ustekinumab, subgroup analyses in French cohort studies have suggested
38 that the benefits of both non-anti-TNF biological agents could be influenced by the latter
39 characteristics[17]. Great caution is nevertheless necessary given the absence of controlled data.
40 Indeed, in another similar study, subgroup analysis did not confirm those data showing the
41 lesser effectiveness of vedolizumab than ustekinumab in non-stricturing and non-penetrating
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Our study had inherent limitations. First, the choice of vedolizumab and ustekinumab is negatively impaired by French reimbursement considerations as well current use of anti-TNF in 58.9% of cases. We reduced this bias by stratifying multivariable analysis on prior and current biological therapy. Our study enrolled participants solely from tertiary referral academic medical centres. Therefore, the study sample may not be representative of the overall CD population, and the treating physicians' preferences may not reflect that of the general gastroenterologist population. Indeed, while most patients were treated with biologics, approximately half of them were treated with intravenous biological agents. However, patients with more severe CD are probably the best target population for discussions about contraindications to biologics and alternative strategies. In this study, we included patients receiving ongoing maintenance therapy with anti-TNFs, vedolizumab and ustekinumab, which could have influenced physicians' preference in favour of the latter drugs. However, those parameters were included in the multivariate analysis to ensure reliable results. Our questionnaire was designed without a validated methodology but included all relevant topics in the field of IBD-related disability. Finally, we acknowledge missing data despite the use of a brief questionnaire.

In conclusion, up to 11.5% of patients with Crohn's disease cannot be treated with anti-TNFs because of contraindications, which can be either absolute and definitive or relative and transient. Physicians are more likely to use ustekinumab when anti-TNFs are contraindicated. The choice of an alternative therapy to anti-TNFs trends more in favour of vedolizumab in cases of Crohn's disease with a ulcerative colitis-like phenotype. Even in an unrestricted reimbursement setting, anti-TNFs remained the preferred first-line biological therapy choice of physicians except in cases with significant comorbidities.

TABLE AND FIGURE LEGENDS

FIGURE LEGEND

Figure 1: Prevalence of contraindications to anti-TNF in 1293 patients with Crohn's disease

TABLE LEGEND

Table 1: Demographic and disease and medication characteristics of 1314 patients with Crohn's disease.

Table 2: Predictors of the choice of vedolizumab as alternative biological agent in case of contraindication to anti-TNF in 632 patients with Crohn's disease who filled out the survey questionnaire

Table 3: Predictors of the choice of ustekinumab as alternative biological agent in case of contraindication to anti-TNF in 632 patients with Crohn's disease who filled out the survey questionnaire

Table 4: Predictors of the choice of anti-TNF assuming that patients were naïve of biological therapy and in the setting of unrestricted reimbursement in 1161 patients with Crohn's disease who filled out the survey questionnaire

SUPPLEMENTARY FILES

Table S1: Demographic and occupational characteristics of investigators.

Figure S1: Complete questionnaire

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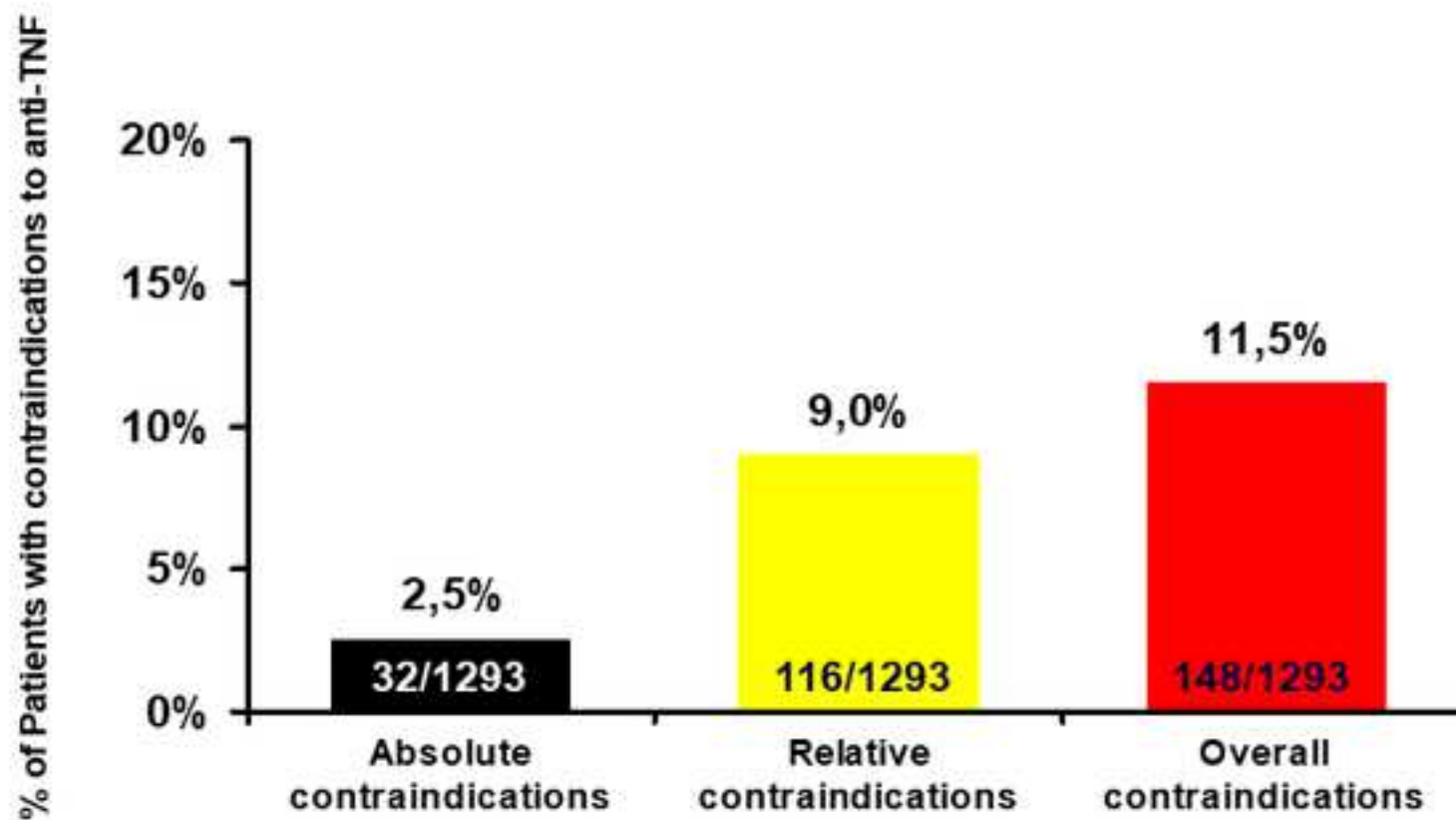


Table 1: Demographic and disease and medication characteristics of 1314 patients with Crohn's disease.

Characteristic	Overall population (n = 1314)	Missing values (%)
Age at diagnosis, years	40.0 [30.0-52.0]	0.9%
Male gender, no (%)	47.3%	1.4%
Duration of Crohn's disease, years	12.3 [6.3-20.3]	5.4%
Smoking habits, no (%)		
Current smoker	53.7%	9.1%
Past smoker	24.0%	
Never smoker	22.3%	
Age at diagnosis, no (%)		
A1: ≤16 years	16.8%	6.2%
A2: 17 – 40 years	66.8%	
A3: > 40 years	16.4%	
Crohn's disease location, no (%)		
L1: ileal	35.1%	5.6%
L2: colonic	22.1%	
L3: ileocolonic	42.2%	
L4: upper GI tract	8.5%	
Crohn's disease behaviour, no (%)		
B1: non-fistulizing non-obstructing	48.4%	12.4%
B2: obstructing	28.0%	
B3: fistulizing	23.6%	

P: perianal lesions	33.6%	7.8%
History of intestinal resection, no (%)	41.1%	2.9%
History of perianal surgery, no (%)	23.3%	5.5%
Patient global assessment of clinical remission, no (%)	71.0%	6.7%
History of medical treatment		
5-ASA	57.2%	
Thiopurine	78.2%	
Methotrexate	24.8%	
Infliximab	68.3%	0.7%
Adalimumab	53.0%	
Ustekinumab	19.8%	
Vedolizumab	11.9%	
Tofacitinib	0.8%	
Current treatment		
None	14.8%	
5-ASA	2.5%	
Immunomodulator alone	4.5%	
Anti-TNF	58.9%	0.7%
Ustekinumab	11.3%	
Vedolizumab	6.6%	
Tofacitinib	0.6%	

5-ASA: 5-aminosalicylic acid; TNF: tumor-necrosis factor; BMI: body mass index; GI: gastrointestinal.

Variables are presented as n (%), mean \pm standard deviation or median (interquartile range).

Table 2: Predictors of the choice of vedolizumab as alternative biological agent in case of contraindication to anti-TNF in 632 patients with Crohn's disease

	Choice of vedolizumab (n = 151)	Other choice (n = 481)	P	HR [95%CI] on multivariate analysis	P
Age > 60 years	22.7%	12.4%	0.004	1.91 [1.06-3.45]	0.03
Male gender	40.7%	51.7%	0.02	-	NS
Crohn's disease duration > 10 years	65.2%	57.2%	0.10	-	NS
L1 phenotype	25.0%	36.8%	0.009	-	NS
L2 phenotype	36.8%	17.3%	<0.001	3.28 [1.96-5.52]	< 0.001
B1 phenotype	57.1%	45.7%	0.02	-	NS
B2 phenotype	22.6%	31.1%	0.06	-	NS
perianal lesions	21.5%	35.1%	0.003	0.39 [0.22-0.69]	0.001
History of anti-TNF therapy	83.4%	89.2%	0.07	-	NS
History of vedolizumab therapy	23.2%	10.9%	< 0.001	-	NS
History of ustekinumab therapy	18.5%	18.4%	1.00	-	NS

Current anti-TNF therapy	49.0%	63.0%	0.003	-	NS
Current vedolizumab therapy	20.5%	5.4%	< 0.001	-	NS
Current ustekinumab therapy	6.0%	10.9%	0.08	-	NS

HR: hazard ratio; CI: confidence interval. Hazard ratio (HR) with 95% confidence interval (CI) was estimated using binary logistic regression.

Table 3: Predictors of the choice of ustekinumab as alternative biological agent in case of contraindication to anti-TNF in 632 patients with Crohn's disease

	Choice of ustekinumab (n = 478)	Other choice (n = 154)	P	HR [95%CI] on multivariate analysis	P
Age > 60 years	12.5%	22.2%	0.006	-	NS
Male gender	51.4%	41.8%	0.04	-	NS
Crohn's disease duration > 10 years	57.1%	65.3%	0.10	-	NS
L1 phenotype	37.0%	24.5%	0.005	1.94 [1.11-3.37]	0.02
L2 phenotype	17.4%	36.1%	< 0.001	0.32 [0.18-0.55]	< 0.001
B1 phenotype	45.5%	57.4%	0.02	-	NS
B2 phenotype	31.1%	22.8%	0.07	-	NS
perianal lesions	35.4%	21.0%	0.002	2.49 [1.45-4.29]	0.001
History of anti-TNF therapy	89.1%	83.8%	0.09	-	NS
History of vedolizumab therapy	10.5%	24.0%	< 0.001	-	NS
Current anti-TNF therapy	63.4%	48.1%	0.001	2.77 [1.71-4.50]	< 0.001

Current vedolizumab therapy	5.0%	21.4%	< 0.001	-	NS
Current ustekinumab therapy	10.9%	5.8%	0.08	-	NS

HR: hazard ratio; CI: confidence interval. Hazard ratio (HR) with 95% confidence interval (CI) was estimated using binary logistic regression.

Table 4: Predictors of the choice of anti-TNF assuming that patients were naïve of biological therapy and in the setting of unrestricted reimbursement in 1161 patients with Crohn’s disease who filled out the survey questionnaire

	Choice of anti-TNF (n = 908)	Choice of other biological agent (n = 253)	P	HR [95%CI] on multivariate analysis	P
Age > 60 years	10.9%	23.4%	< 0.001	0.45 [0.29-0.71]	0.001
Male gender	47.8%	41.6%	0.09	-	NS
L1 phenotype	33.3%	42.8%	0.007	-	NS
L2 phenotype	44.5%	33.9%	0.004	-	NS
B1 phenotype	46.7%	53.4%	0.08	-	NS
B3 phenotype	24.7%	14.8%	0.001	1.87 [1.36-2.47]	0.009
perianal lesions	37.1%	20.2%	< 0.001	2.39 [1.57-3.64]	< 0.001
Any contraindication to anti-TNF therapy	7.4%	20.2%	< 0.001	0.35 [0.22-0.56]	< 0.001
History of anti-TNF therapy	89.5%	82.2%	0.002	-	NS
History of vedolizumab therapy	10.4%	19.0%	< 0.001	-	NS
History of ustekinumab therapy	19.4%	25.0%	0.06	-	NS

Current anti-TNF therapy	64.2%	40.3%	< 0.001	2.15 [1.53-3.03]	< 0.001
Current vedolizumab therapy	5.1%	12.3%	< 0.001	-	NS
Current ustekinumab therapy	10.3%	19.0%	< 0.001	-	NS

HR: hazard ratio; CI: confidence interval. Hazard ratio (HR) with 95% confidence interval (CI) was estimated using binary logistic regression.

This document certifies that the manuscript

Determinants of physicians' perception of anti-TNF contraindication: a cross-sectional survey from the GETAID

prepared by the authors

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INFORMATIONS CONCERNANT LE PATIENT

Âge : Sexe : F H Lieu de suivi : Centre Hospitalier Universitaire
 Centre Hospitalier Régional

INFORMATIONS SUR LA MALADIE DE

Type de MICI : Maladie de Crohn
 RCH

Topographie : L1 E1
 L2 E2
 L3 E3
 L4

Phénotype : B1
 B2
 B3
 LAP

Année de diagnostique :

Tabagisme : Actif Sevré Non-fumeur

Antécédents de chirurgie de résection intestinale : Oui Non

Antécédents de chirurgie anopérinéale : Oui Non

En cours de rémission clinique : Oui Non

TRAITEMENT

Parmi les traitements suivants, cochez les cases correspondantes :

Corticoïdes (Solupred®, Cortancyl®, Entocort®, Micikort®) A déjà eu ce traitement En cours de traitement

5-ASA (Pentasa®, Rowasa®, Fivasa®, Dipentum®, Salazopyrine®) A déjà eu ce traitement En cours de traitement

Thiopurines (Imurel®, Purinethol®) A déjà eu ce traitement En cours de traitement

Methotrexate (Méthotrexate®, Metoject®, Imeth®, Ledertrexate®, Nordimet®, Novatrex®) A déjà eu ce traitement En cours de traitement

Anti-TNF intraveineux (Remicade®, Inflectra®, Flixabi®, Remsima®) A déjà eu ce traitement En cours de traitement

Anti-TNF sous-cutané (Humira®, Amgevita®, Imraldi®, Halimatoz®, Hulio®, Hyrimoz®, Hefiya®, Solymbic®, Idacio®) A déjà eu ce traitement En cours de traitement

Ustekinumab (Stelara®) A déjà eu ce traitement En cours de traitement

Vedolizumab (Entyvio®) A déjà eu ce traitement En cours de traitement

Tofacitinib (Xeljanz®) A déjà eu ce traitement En cours de traitement

CONTRE-INDICATION ABSOLUE AUX

Chez ce patient, existe-t-il une contre-indication absolue aux anti-TNF ?

Oui Non

Si oui,

- Insuffisance cardiaque NYHA 3-4
- Tuberculose active
- Sclérose en plaque
- Hépatite B active

Autre :

Chez ce patient, existe-t-il une contre-indication relative aux anti-TNF ?

Oui Non

Si oui, cochez les cases correspondantes :

- | | |
|--|---|
| <input type="checkbox"/> Tuberculose latente | <input type="checkbox"/> Lupus érythémateux systémique |
| <input type="checkbox"/> VIH | <input type="checkbox"/> Insuffisance cardiaque NYHA <3 |
| <input type="checkbox"/> Risque infectieux | <input type="checkbox"/> Antécédents de cancer |
| <input type="checkbox"/> Pathologies associées | <input type="checkbox"/> < 5 ans <input type="checkbox"/> > 5 ans |

S'il existe des risques infectieux : lesquels ?

Si le patient présente une/des pathologie(s) associée(s), précisez :

Si vous estimez qu'il existe une contre-indication relative aux anti-TNF et que ce patient justifie d'une biothérapie ou d'un changement de biothérapie, quel traitement prescririez-vous ?

Vedolizumab (Entyvio®) Ustekinumab (Stelara®) Tofacitinib (Xeljanz®)

Autre :

Si vous deviez (re-)discuter de la première ligne de biothérapie chez ce patient, quel serait votre choix préférentiel (indépendamment de la problématique du remboursement) ?

- Vedolizumab (Entyvio®)
- Ustekinumab (Stelara®)
- Tofacitinib (Xeljanz®)
- Anti TNF alpha IV (Remicade®, Inflectra®, Flixabi®, Remsima®)
- Anti TNF alpha SC (Humira®, Amgevita®, Imraldi®, Halimatoz®, Hulio®, Hyrimoz®, Hefiya®, Solymbio®, Idacio®)

Autre :

MERCI POUR VOTRE PARTICIPATION

Ce questionnaire est élaboré par le GETAID dans le cadre d'une enquête concernant les patients atteints d'une maladie de Crohn, pour mieux comprendre leur maladie et leur prise en charge. Les informations fournies serviront exclusivement à cette enquête.

Le fichier informatique utilisé pour cette recherche est mis en œuvre conformément à la réglementation française (Loi Informatique et Libertés modifiées) et européenne (Règlement Général sur la Protection des Données – RGPD). Le GETAID s'engage à assurer la confidentialité des informations fournies.

En cas de difficulté dans l'exercice de vos droits, vous pouvez saisir le Délégué à la Protection des Données du GETAID à l'adresse suivante : GETAID – 50, rue Richer 75009 Paris, qui pourra notamment vous expliquer les voies de recours dont vous disposez auprès de la CNIL.

Table S1: Demographic and occupational characteristics of investigators.

Characteristic	Overall population (n = 1314)
Age at diagnosis, years	43.5 [38.0-51.3]
Male gender (%)	57.7%
Seniority (%)	
<5 years	0%
5-10 years	23.1%
10-15 years	34.6%
>15 years	42.3%
Weekly IBD patient encounter (%)	
<5	0
6-10	7.7%
>10	92.3%
Decision making process for biologics	

Mostly during patient encounter	80.8%
Mostly during multidisciplinary meeting	0%
Both	19.2%
Therapeutic objective (%)	
Clinical remission	0%
Steroid-free clinical remission	4.9%
Steroid-free clinical remission plus mucosal healing	96.1%
Steroid-free clinical remission plus histological healing	0%
Most important factor in treatment choice (%)	
Effectiveness	100%
Safety	0%
Time to efficacy	0%
Mode of administration	0%
Treatment cost	0%

Variables are presented as n (%), mean \pm standard deviation or median (interquartile range).