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Alimentary Tract

Thiopurines have no impact on outcomes of Crohn's disease patients beyond 12 months of maintenance treatment with infliximab

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ABSTRACT

Background: The emergence of new treatments the inflammatory bowel diseases (IBD) raised questions regarding the role of older agents, namely thiopurines.
Aims: To clarify the benefits of combination treatment with thiopurines on Crohn's disease (CD) patients in the maintenance phase of infliximab.
Methods: In this analysis of the 2-year prospective multicentric DIRECT study, patients were assessed in terms of clinical activity, faecal calprotectin (FC), C-reactive protein (CRP), and infliximab pharmacokinetics. A composite outcome based on clinical- and drug-related items was used to define treatment failure.
Results: The study included 172 patients; of these, 35.5 % were treated with combination treatment. Overall, 18 % of patients achieved the composite outcome, without statistically significant differences between patients on monotherapy and on combination treatment (21.6% vs 11.5 %, $p = 0.098$). Median CRP, FC, and infliximab pharmacokinetic parameters were similar in both groups. However, in the sub-analysis by infliximab treatment duration, in patients treated for less than 12 months, the composite outcome was reached in fewer patients in the combination group than in the monotherapy group (7.1% vs 47.1 %, $p = 0.021$).
Conclusion: In CD patients in maintenance treatment with infliximab, combination treatment does not seem to have benefits over infliximab monotherapy beyond 12 months of treatment duration.

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1. Introduction

In the last years, the therapeutic landscape of inflammatory bowel disease (IBD) has been evolving rapidly, with the approval of new drugs with novel mechanisms of action and several others in the pipeline [1]. For Crohn's disease (CD), gone are the days in which steroids and immunomodulators were the main weapons in the IBDologists armamentarium. As such, the current role of these older agents in the therapeutic algorithm of IBD has been increasingly questioned, particularly due to the more affordable prices of biosimilar drugs.

In the case of thiopurines, recent real-world studies demonstrated that monotherapy with these drugs had durable effectiveness in only about one-third of the CD patients [2,3]. However, other authors have argued that thiopurines remain an effective, safe, and durable treatment option for IBD, even in the era of biologics [4]. On the other hand, since the landmark SONIC trial, combination treatment with infliximab and azathioprine has been established as superior to monotherapy with either of the drugs in inducing clinical and endoscopic remission in CD patients [5]. Both European and American guidelines recommend combination treatment with a thiopurine and infliximab to induce remission in patients with moderate-to-severe CD [6]. Real-life studies corroborate the efficacy of this strategy; in a population-based study evaluating new users of anti-TNF with both CD (n = 852) and ulcerative colitis (n = 303), combination treatment with immunomodulators was associated with a significant decrease in the likelihood of treatment ineffectiveness in CD, with a decrease of about 40 % in hospitalizations, surgeries and corticosteroid use [7]. Still, the optimal duration of combination treatment remains an unanswered question. In an open-label controlled trial with CD patients treated with infliximab, continuation of combination treatment beyond 6 months did not show additional clinical benefit, including mucosal healing. However, it was associated with higher infliximab trough levels and lower C-reactive protein (CRP) values [8]. A Cochrane systematic review that evaluated clinical relapse after azathioprine discontinuation from a combination treatment regimen with infliximab (compared with patients who continued combination treatment), did not find differences between groups [9]. More recently, the SPARE trial, which included patients on combination treatment with infliximab and an immunosuppressant (thiopurine or methotrexate) for at least 8 months, provided additional data on this matter [10]. The study compared the relapse rate and time spent in remission in CD patients continuing combination treatment with those stopping either infliximab or immunomodulators. The results showed that the withdrawal of the immunosuppressant treatment was not associated with an increased risk of relapse nor with drug immunogenicity.

In this context, the clarification of the added advantages of keeping combination treatment during the maintenance phase of infliximab treatment would benefit the treatment selection process and improve patient care. At the same time, it would allow to more effectively balance the benefits of combination treatment against its potential side effects, namely the risk of serious infections and malignancies [11].

In this analysis of the 2-year long prospective observational DIRECT study—a study to investigate the correlation of faecal calprotectin with serum **D**rug levels and development of ant**I**-d**R**ug antibodi**E**s amongst adult patients with inflammatory bowel disease receiving anti-TNF-alfa treatment or vedolizumab treatment—, we aimed at clarifying the benefits of combination treatment on the maintenance phase of infliximab in CD patients, in comparison with patients treated with infliximab in monotherapy.

2. Methods

2.1. Study design

DIRECT was a multicentre, prospective, real-world study that investigated the correlation between faecal calprotectin, serum drug levels, and the development of anti-TNF antibodies in adult IBD patients receiving anti-TNF-α treatment. Participants were recruited from 8 Portuguese specialized IBD centres, between May 2016 and October 2019, and followed for approximately 2 years. Inclusion criteria were: i) male or female patients with 18 years or older; ii) registered in the Portuguese IBD group (GEDII [Group of Studies in Inflammatory Bowel Disease]) registry; iii) diagnosed with moderate to severe active CD or UC; and iv) receiving anti-TNF agents. The current analysis considered all DIRECT study CD patients in the maintenance phase ($\geq$14 weeks) of infliximab, at a standard dose and interval (5 mg/kg every 8 weeks) prior to study entry, either in monotherapy or in combination treatment with a thiopurine (azathioprine or mercaptopurine). Patients treated with methotrexate were excluded.

2.2. Data collection

Patients were evaluated at each infliximab infusion, with assessment of their reported health status and collection of blood and stool samples. Supplementary Figure 1 details the collected data, at each time point.

At each visit, patients were instructed to fill out a questionnaire (patient-reported outcome 2 [PRO-2]) aimed at the evaluation of abdominal pain and soft/liquid stool frequency, in the week before each infusion; final scores were determined as a 7-day average [12].

Before each treatment, blood was collected for assessment of CRP and infliximab and anti-infliximab levels, at a central laboratory. CRP was determined using a highly sensitive assay (Konelab/T Series CRP High Sensitivity Control; Thermo Scientific, Vantaa, Finland) and infliximab levels were measured via the Quantum Blue infliximab quantitative lateral flow assay (Buhlmann, Schönenbuch, Switzerland). Anti-infliximab levels were measured through a drug-tolerant in-house enzyme-linked immunosorbent assay (anti-human lambda chain assay; 1.2–100 µg/mL) [13]. Anti-infliximab levels were considered negative below 1.7 µg/mL. In the analysis, we considered the mean values of all the measurements of infliximab and anti-infliximab levels prior to infliximab optimization (i.e. while the patients were still in the standard dose and interval). The investigators did not have immediate access to the results so that treatment decisions were not affected.

A stool sample was collected at the same time point as blood samples and immediately sent to a central laboratory for the evaluation of faecal calprotectin (FC), using the Quantum Blue Kit (Bühlmann, Schönenbuch, Switzerland).

Median levels of CRP and FC for each patient were used in the statistical analysis.

2.3. Outcomes and definitions

Patients were considered to be in combination treatment when taking azathioprine or mercaptopurine for 6 weeks or more before study baseline, keeping the treatment for at least half of the follow-up period. The remaining patients were considered to be on infliximab monotherapy.

Treatment optimization was defined as an increase in treatment dose above 5 mg/kg and/or shortening of the interval between infusions to less than every 8 weeks.

A composite outcome adapted from previous studies [14–16] was used to define disease progression; it was based on clinical-related items (first occurrence of at least one of the following: abdominal surgery; IBD-related hospitalization; or new fistulae, abscess, or stricture) and drug-related items (first occurrence of at least one of the following: one course of oral corticosteroids or more than 10 mg of prednisolone daily; *de novo* azathioprine or methotrexate; switch of biological therapy owing to clinical unresponsiveness [to adalimumab, golimumab, vedolizumab, or ustekinumab]; or azathioprine dose increase not related to weight fluctuation). These criteria were only valid when occurring during the follow-up of each patient, between the first and last study visits. Any treatment change was solely based on clinical judgement, as investigators were unaware of this composite outcome during follow-up.

Persistent inflammation was defined as a FC above 250 µg/g, over 2 consecutive visits [16].

As the impact of combination treatment may vary according to the dose of thiopurine, we performed a sub-analysis of the aforementioned outcomes by azathioprine dose intervals (<1.5 mg/kg; ≥1.5 and <2 mg/kg; and ≥2 mg/kg). The duration of infliximab treatment may also influence the eventually added benefit of thiopurines, as this may only be relevant in the first 6 to 12 months of treatment [8,17]. As such, we also performed a sub-analysis in the combination group by infliximab treatment duration, using two different cut-offs: 6 months and 12 months; the outcomes for each of these subgroups were compared with those of infliximab monotherapy.

2.4. Statistical analysis

Categorical variables were summarized by absolute and relative frequencies. Associations between categorical variables were evaluated with Chi-square and Fisher's exact tests. Continuous variables were described by median and interquartile range (IQR). Mann-Whitney U test was used for associations between continuous variables. Linear relationships between two variables were calculated with the Spearman rank correlation coefficient.

Time since the first visit until the occurrence of the composite outcome was estimated using Kaplan-Meier curves and compared between the combination treatment and monotherapy with infliximab groups using the Log Rank test.

All reported p values were 2-sided, with the significance level set at 5 %. Data were processed using the IBM SPSS Statistics for Windows version 26.0. The study was reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. All authors had access to study data and reviewed and approved the final manuscript.

2.5. Ethics

The participation of all patients was voluntary, and all patients signed a written informed consent. The study was centrally monitored, conducted according to the Declaration of Helsinki principles, and approved by the ethics committee of each institution and by the Portuguese Data Protection Authority.

3. Results

3.1. Patient characteristics

From the 332 patients treated with infliximab in the DIRECT study, 172 fulfilled the inclusion criteria for this analysis. Of these, 61 patients (35.5 %) were treated in combination treatment (60 with azathioprine and 1 with mercaptopurine).

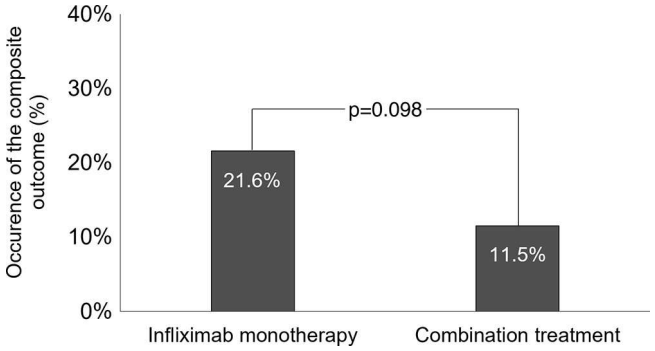

Fig. 1. Occurrence of the composite outcome in the infliximab monotherapy and combination treatment groups.

No significant differences were found regarding baseline characteristics between patients in combination treatment and in monotherapy with infliximab (Table 1). In both groups, most patients were male, with a median age of 41 years and a median disease duration of 9 years. Infliximab was the first biological treatment for most patients, with a median duration of treatment of 37.5 months. Patients previously exposed to another biological (7.2 % in the monotherapy group and 4.9 % in the combination therapy group) had been treated with adalimumab. In both groups, most patients had previously been treated with thiopurines, the majority in the combination treatment group (88.3% vs 98.4 % in the monotherapy group and combination therapy group, respectively; $p = 0.020$).

3.2. Outcomes

3.2.1. Composite outcome

Overall, 18 % of patients achieved the composite outcome (Table 2). The results did not show statistically significant differences in the achievement of the composite outcome during follow-up between patients on infliximab monotherapy and on combination treatment (Fig. 1). Additionally, there were no statistically significant differences until the occurrence of the composite outcome between both groups (Fig. 2) In the sub-analysis of the drug-related and clinical-related items of the composite outcome, again, no statistically significant differences between infliximab monotherapy and combination treatment were found.

3.3. Persistent inflammation

The median CRP and FC levels were also similar in the infliximab monotherapy group and in the combination treatment group (Table 2). Persistent inflammation was present in 49.4 % of our cohort, with no significant differences between the infliximab monotherapy group and the combination treatment group.

On the other hand, we could detect a significant, albeit weak to moderate, correlation between the mean levels of infliximab and CRP levels ($r = -0.378$, $p < 0.001$) and FC ($r=-0.259$, $p < 0.001$). There was also a significant albeit weak correlation between the mean levels of anti-infliximab antibodies and CRP levels ($r = 0.312$, $p < 0.0\ 01$) and FC ($r = 0.188$, $p = 0.014$).

3.4. Infliximab pharmacokinetics

The analysis of infliximab pharmacokinetics in patients in combination and monotherapy treatment, showed that median infliximab trough levels were slightly higher in the monotherapy group, but without statistical significance. Anti-infliximab antibodies were also similar in both groups (Fig. 3).

Table 1
Characteristics of the study population.

	Total patients (n = 172)	IFX monotherapy (n = 111)	Combination treatment (thiopurines + IFX) (n = 61)	p value
Age, y - median (Q1, Q3)	41.0 (31.0–49.0)	41.0 (32.0–50.0)	41.0 (29.0–48.5)	0.402
Age at diagnosis, y – median (Q1-Q3)*	25.0 (20.0–34.0)	26.0 (20.0–35.0)	24.0 (17.25–32.0)	0.241
Disease duration, y -median (Q1-Q3)*	9.0 (6.00–17.00)	9.00 (6.0–16.25)	9.50 (5.0–18.0)	0.969
Male, *n* (%)	92 (53.5 %)	65 (58.6 %)	27 (44.3 %)	0.072
Smoking habits, *n* (%)				0.661
Never smoked	90 (52.3 %)	60 (54.1 %)	30 (49.2 %)	
Less than 10/d	25 (14.5 %)	17 (15.3 %)	8 (13.1 %)	
Between 10–20/d	15 (8.7 %)	8 (7.2 %)	7 (11.5 %)	
More than 20/d	3 (1.7 %)	1 (0.9 %)	2 (3.3 %)	
Former smoker	39 (22.7 %)	25 (22.5 %)	14 (23.0 %)	
Family history of IBD – *n* (%)**	21 (12.2 %)	14 (15.9 %)	7 (16.3 %)	0.432
Disease location, *n* (%)				0.494
L1	69 (40.1 %)	47 (42.3 %)	22 (36.1 %)	
L2	26 (15.1 %)	18 (16.2 %)	8 (13.1 %)	
L3	77 (44.8 %)	46 (41.4 %)	31 (50.8 %)	0.494***
L4	25 (14.5 %)	17 (15.3 %)	8 (13.1 %)	0.695****
Disease behaviour, *n* (%)				0.473
B1	85 (49.4 %)	53 (47.7 %)	32 (52.5 %)	
B2	34 (19.8 %)	25 (22.5 %)	9 (14.8 %)	
B3	53 (30.8 %)	33 (29.7 %)	20 (32.8 %)	
Perianal disease, *n* (%)	51 (29.7 %)	33 (29.7 %)	18 (29.5 %)	0.976
Steroid dependent, *n* (%)	52 (30.2 %)	32 (28.8 %)	20 (32.8 %)	0.589
Steroid resistant, *n* (%)	4 (2.3 %)	4 (3.6 %)	0 (0.0 %)	0.298
Previous surgery, *n* (%)	90 (52.3 %)	58 (52.3 %)	32 (52.5 %)	0.438
Previous treatments				
Steroids, *n* (%)	84 (48.8 %)	55 (49.5 %)	29 (47.5 %)	0.801
Mesalazine, *n* (%)	97 (56.4 %)	64 (57.7 %)	33 (54.1 %)	0.652
Thiopurines, *n* (%)	158 (91.9 %)	98 (88.3 %)	60 (98.4 %)	0.020
Biologics, *n* (%) Adalimumab	11 (6.4 %)	8 (7.2 %)	3 (4.9 %)	0.748
Duration of infliximab treatment, months (Q1-Q3)*	37.5 (16.25–70.75)	41.0 (20.0–72.0)	35 (14.5–64.0)	0.087

* 2 missing values (1 from monotherapy and 1 from combination treatment).
** 41 missing values (23 from IFX monotherapy and 18 from combination treatment).
*** L1 vs L2 vs L3.
**** L4 yes versus no
IFX: infliximab.

Table 2
Study outcomes in infliximab monotherapy and combination subgroups.

	Total patients (n = 172)	IFX monotherapy (n = 111)	Combination treatment (thiopurines + IFX) (n = 61)	p value
Composite outcome, *n* (%)	31 (18.0 %)	24 (21.6 %)	7 (11.5 %)	0.098
Clinical related items	16 (0.3 %)	13 (11.7 %)	3 (4.9 %)	0.142
Drug related items	19 (11.0 %)	14 (12.6 %)	5 (8.2 %)	0.377
Median FC µg/g, median (Q1–Q3)*	172.00 (83.00–412.00)	176.25 (77.00–408.75)	149 (94.75–454.50)	0.686
Median CRP g/L, median (Q1–Q3)	2.25 (0.60–4.62)	2.17 (0.90–4.85)	2.25 (0.88-4-50)	0.814
Persistent inflammation, *n* (%)	85 (49.4 %)	56 (50.5 %)	29 (47.5 %)	0.715
Dose and/or interval optimization during follow-up, *n* (%)	49 (28.5 %)	34 (30.6 %)	15 (24.6 %)	0.401

*3 missing values (3 from IFX monotherapy).
IFX: infliximab.

During follow-up, either the dose of infliximab was increased and/or the infusion interval was shortened in 28.5 % of the patients, without statistically significant differences in the need for infliximab optimization between groups.

3.5. Sub-analysis by azathioprine dose, duration of treatment with infliximab, and previous CD-related surgery

Azathioprine dose

Of the 60 patients treated in combination treatment with azathioprine, 9 (15 %) were treated with a dose lower than 1.5 mg/kg, 21 (35 %) with a dose ranging from 1.5 to 2 mg/kg, and 30 (50 %) with a dose equal or superior to 2 mg/kg. When comparing the outcomes of each dose interval with those of the infliximab monotherapy subgroup, no statistically significant differences were detected (Supplementary Table 1). A numerically lower percentage of patients in the highest dose of azathioprine reached the composite outcome when compared with infliximab monotherapy (6.7% vs 21.6 %, respectively, p = 0.252), but without statistical significance.

Concerning the pharmacokinetics of infliximab, no statistically significant differences between each dose of azathioprine and the infliximab monotherapy group were observed. In the combination treatment group, patients with the lower doses of azathioprine presented the highest levels of infliximab and the lowest levels of antibodies.

3.6. Duration of treatment with infliximab

Only 19 patients were treated with infliximab for a period equal to or inferior to 6 months; of these, 12 (63.2 %) were in monotherapy and 7 (36.8 %) in combination treatment (Supplementary Ta-

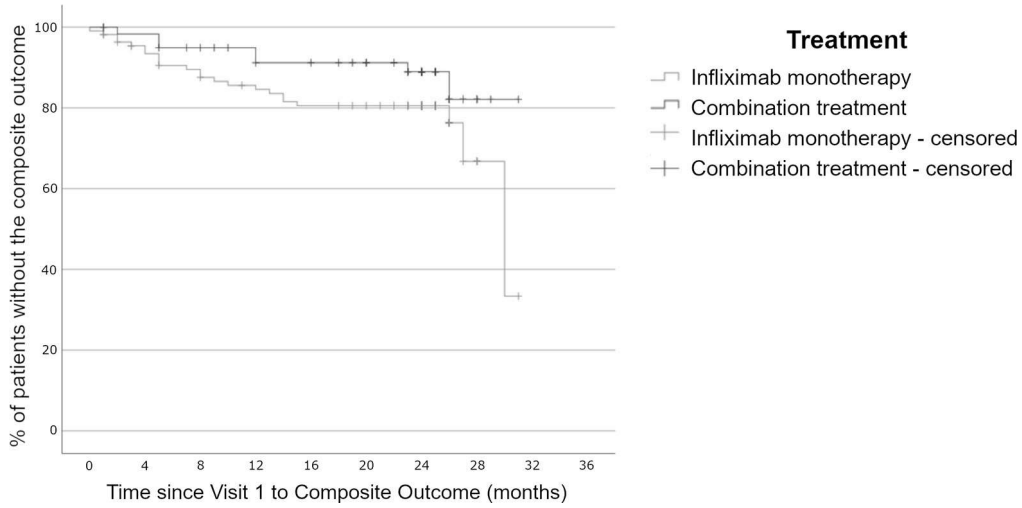

Fig. 2. Kaplan-Meier Survival Curves of the Time until Composite Outcome in patients treated with combination treatment and patients in monotherapy with Infliximab ($p = 0.107$).

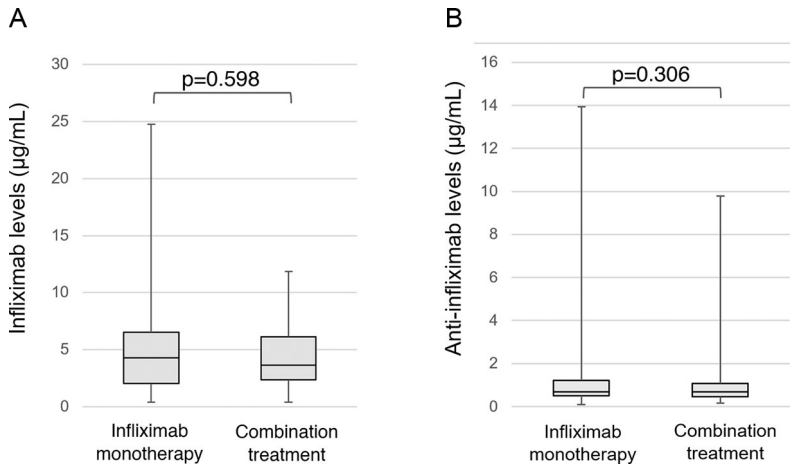

Fig. 3. Pharmacokinetics of infliximab in infliximab monotherapy and combination treatment subgroups (A: infliximab levels; B: anti-infliximab levels).

ble 2). A higher percentage of patients in monotherapy reached the composite outcome (50.0% vs 14.3 %, $p = 0.173$), had persistent inflammation (75.0% vs 57.1 %, $p = 0.617$), and showed a need to optimize treatment (41,7 % vs 14.3 %, $p = 0.333$), but without statistical significance. CRP and FC levels were also numerically lower in the combination treatment group [CRP: 2.40 mg/L (0.93–5.95) vs 1.3 mg/L (0.70–4.35), $p = 0.237$; FC: 422 µg/g (174–750) vs 156 µg/g (99–258), $p = 0.094$], but without statistical significance. On the other hand, in the subgroup of patients treated with infliximab for more than 6 months (153 patients; 64.7 % in monotherapy, and 35.3 % in combination treatment), these outcomes were similar in monotherapy and combination treatment.

Thirty-one patients were treated with infliximab for a period equal to or inferior to 12 months; of these, 17 (54.8 %) were in monotherapy and 14 (45.2 %) were in combination treatment. The composite outcome was reached in fewer patients in the combination group than in the monotherapy group (7.1% vs 47.1 %, $p = 0.021$), with statistical significance. The median CRP and FC levels were also lower in the combination group, but the results were not statistically significant. On the other hand, in the group of 141 patients treated for more than 12 months with infliximab at the time of enrolment, outcomes were similar in the monotherapy and combination treatment groups.

Concerning the pharmacokinetic parameters of infliximab, our analysis did not retrieve statistically significant differences in either median infliximab levels or anti-infliximab levels between the infliximab monotherapy and the combination treatment groups; this is valid for all time points, using 6 or 12 months as cut-offs.

3.7. Previous CD-related surgery

As thiopurines have been shown to be effective in the prevention of post-operative recurrence of CD [18], we performed a subanalysis on the 90 patients with previous CD-related surgery. In this subgroup, there were no differences in the occurrence of the composite outcome between patients in infliximab monotherapy and combination treatment (22.4% vs 12.5 %, $p = 0.250$). There were also no differences between both groups in terms of persistent inflammation (50.0 % of patients in both groups had persistent inflammation) or need for infliximab optimization (32.7% vs 28.1 % in the infliximab monotherapy and combination group, respectively, $p = 0.649$).

4. Discussion

Despite the long experience with thiopurines in IBD, the emergence of an increasing number of safe and effective options for the treatment of these disorders has posed questions regarding the role of thiopurines in the therapeutic algorithm. Shall these drugs

still be used in monotherapy? Will their benefits be evident only in combination therapy? Should they be used at all?

In an international survey with the participation of 465 physicians, in which more than one quarter was included in the group of "IBD experts", most participants declared to still use thiopurines both in monotherapy and in combination treatment in CD, but mostly in combination treatment [19]. Even if in the future the use of thiopurines became restricted to an adjunct treatment to infliximab, we would still be left with the question: how much and for how long?

In this study, we demonstrated that in CD patients in maintenance treatment with infliximab, combination treatment was not superior to infliximab monotherapy. In the SONIC trial, the landmark study that demonstrated the superiority of combination treatment over infliximab or azathioprine in monotherapy, all patients were bio- and immunomodulator-naïve. In the prospective personalized anti-TNF-therapy in CD patients (PANTS) study, patients were also recruited at the first anti-TNF exposure. Other studies showing increased effectiveness of combination treatment of anti-TNF with immunomodulators also included patients in their first exposure to this class of drugs [7]. In contrast, in the present study, the mean duration of treatment at the time of enrolment was 37.5 months, which may explain the lack of impact of combination treatment. In fact, our results hinted at a favourable effect of combination treatment when used for the first 6 to 12 months of treatment with infliximab, with no benefit beyond these cut-offs. This is in line with previous studies in which it was demonstrated that no additional clinical benefit derived from maintaining combination treatment beyond 6 months [8] or 12 months [17]. This "expiry date" for a beneficial impact of thiopurines as an adjunct to infliximab may be related to the development of infliximab immunogenicity. The risk for the development of anti-infliximab antibodies appears to be higher in the first 12 months of treatment [20]. Indeed, many of the benefits of combination treatment are related to the improvement of infliximab pharmacokinetics. In the SONIC trial, patients on combination treatment showed lower incidence of anti-infliximab antibodies and higher trough levels of infliximab [5]. In the PANTS study, which included 955 patients treated with infliximab, combination immunomodulator therapy (with thiopurines or methotrexate) was the main protective factor against immunogenicity. In a post-hoc analysis of the SONIC trial, corticosteroid-free remission at week 26 (CSFR26) was compared across infliximab quartiles between patients in monotherapy and in combination treatment. CSFR26 was not significantly different between groups and was, in fact, achieved in more patients in the monotherapy group for the lower quartile of infliximab concentration. The authors concluded that the improved efficacy of the combination treatment was related to pharmacokinetic effects [21]. If this is the case, proactive dosing of infliximab could, perhaps, obviate the need for immunomodulator addition. However, in our study, we could not find differences in infliximab pharmacokinetics between groups, even in the subanalysis by treatment duration.

The lower prices of biosimilars and the confirmed higher rate of adverse events of combination treatment (serious and opportunistic infections and malignancies such as lymphoma) when compared with monotherapy with either agent [22–24] seem to favour, at least, treatment de-escalation for those in combination treatment, when stable. ECCO topical review on treatment withdrawal recommends considering discontinuation of immunomodulators after at least 1 year of treatment and after sustained clinical and endoscopic remission is reached. Factors influencing the decision of immunomodulator withdrawal after this time frame included trough levels of infliximab and disease characteristics, such as high-risk/refractory disease or patients "at risk" of biological failure [25].

Finally, even though some studies have demonstrated higher cost-effectiveness of combination treatment over monotherapy with infliximab, calculations were based on increased treatment effectiveness and decreased need for treatment optimization [26]. In this study, we could not demonstrate the benefits of combination treatment in either of these points.

This study presents several limitations that deserve to be discussed. The study might be underpowered to detect statistically significant differences between groups. The number of subjects in the population, particularly in subgroup analysis, is too small for conclusive results. Thiopurine metabolites were not measured, so the study lacked an analysis in terms of effective thiopurine metabolite levels. In addition, infliximab trough levels were relatively low in the overall cohort compared with the optimal levels reported in literature [27]. To finalize, the choice of combination treatment or monotherapy with infliximab was made by the treating physician and might be possible that patients with more severe disease were treated with the addition of thiopurines, influencing the results.

In conclusion, in CD patients treated with infliximab for more than 12 months, combination treatment does not seem to have benefits over infliximab monotherapy in terms of clinical outcomes, infliximab pharmacokinetics, and need for treatment optimization. Given the known adverse events of combination treatment, the risk-benefit ratio of this strategy seems to not be favourable in the long-term treatment.

Conflict of interest

PS served as speaker for Janssen and received Congress support from Janssen, Abbvie, Dr. Falk, Norgine and Pfizer.

IR reports personal fees and/or non-financial support from Faes Pharma, Ferring, Pharmakern, Janssen and Takeda, outside the submitted work. She also reports research grants from Abbvie and Ferring, outside the submitted work.

HTS served as speaker for Janssen and received Congress support from Abbvie, Ferring, Janssen, Pfizer, Takeda, Tillots, Dr. Falk and Biogen.

FM served as a speaker and received honoraria from Abbvie, Biogen, Falk, Ferring, Hospira, Janssen, Laboratórios Vitória, Lilly, Pfizer, Merck Sharp & Dohme, Sandoz, Takeda, UCB and Vifor.

All other authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.10.027.

References

[1] Grossberg LB, Papamichael K, Cheifetz AS. Review article: emerging drug therapies in inflammatory bowel disease. Aliment Pharmacol Ther 2022;55:789–804.

[2] Verstockt B, Boets L, Sabino J, Vermeire S, Ferrante M. Thiopurine monotherapy has a limited place in treatment of patients with mild-to-moderate Crohn's disease. Gut 2021;70:1416–18.
[3] Stournaras E, Qian W, Pappas A, et al. Thiopurine monotherapy is effective in ulcerative colitis but significantly less so in Crohn's disease: long-term outcomes for 11 928 patients in the UK inflammatory bowel disease bioresource. Gut 2021;70:677–86.
[4] Rezazadeh Ardabili A, Jeuring S, Mujagic Z, et al. Classic drugs in the time of new drugs: real-world, long-term outcomes of thiopurine monotherapy in 1016 patients with inflammatory bowel disease. Aliment Pharmacol Ther 2022;56:1030–43.
[5] Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. New Engl J Med 2010;362:1383–95.
[6] Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. J Crohn's Colitis 2019;14:4–22.
[7] Targownik LE, Benchimol EI, Bernstein CN, et al. Upfront combination therapy, compared with monotherapy, for patients not previously treated with a biologic agent associates with reduced risk of inflammatory bowel disease-related complications in a population-based cohort study. Clinic Gastroenterol Hepatol 2019;17 1788–98.e2.
[8] Van Assche G, Magdelaine–Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology 2008;134:1861–8.
[9] Boyapati RK, Torres J, Palmela C, et al. Withdrawal of immunosuppressant or biologic therapy for patients with quiescent Crohn's disease. Cochrane Database Syst Rev 2018;5 Cd012540.
[10] Louis E, Resche-Rigon M, Laharie D, et al. Withdrawal of infliximab or concomitant immunosuppressant therapy in patients with Crohn's disease on combination therapy (SPARE): a multicentre, open-label, randomised controlled trial. Lancet Gastroenterol Hepatol 2023;8:215–27.
[11] Beaugerie L, Rahier JF, Kirchgesner J. Predicting, preventing, and managing treatment-related complications in patients with inflammatory bowel diseases. Clinic Gastroenterol Hepatol 2020;18 1324–35.e2.
[12] Khanna R, Zou G, D'Haens G, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Aliment Pharmacol Ther 2015;41:77–86.
[13] Rocha C, Lago P, Fernandes S, et al. Rapid test detection of anti-infliximab antibodies: performance comparison with three different immunoassays. Therap Adv Gastroenterol 2020;13:1756284820965790.
[14] Magro F, Alves C, Lopes J, et al. Histologic Features of Colon Biopsies (Geboes Score) associated with progression of ulcerative colitis for the first 36 months after biopsy. Clinic Gastroenterol Hepatol 2021;19 2567–76.e9.
[15] Magro F, Dias CC, Portela F, et al. Development and validation of risk matrices concerning ulcerative colitis outcomes-Bayesian network analysis. J Crohn's Colitis 2019;13:401–9.
[16] Magro F, Magalhães D, Patita M, et al. Subclinical persistent inflammation as risk factor for Crohn's disease progression: findings from a prospective real–world study of 2 years. Clinic Gastroenterol Hepatol 2022;20 2059–73.e7.
[17] Lambrescak E, Vaysse T, Allez M, et al. Duration of combination therapy and risk of treatment failure in patients with inflammatory bowel disease. Clin Res Hepatol Gastroenterol 2021;45:101503.
[18] Peyrin-Biroulet L, Deltenre P, Ardizzone S, et al. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. Am J Gastroenterol 2009;104:2089–96.
[19] Sousa P, Ministro P, Armuzzi A, et al. Thiopurines: use them or lose them? International survey on current and future use of thiopurines in inflammatory bowel disease. Digest Liver Dis 2021;53:1571–9.
[20] Ungar B, Chowers Y, Yavzori M, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. Gut 2014;63:1258–64.
[21] Colombel JF, Adedokun OJ, Gasink C, et al. Combination therapy with infliximab and azathioprine improves infliximab pharmacokinetic features and efficacy: a post hoc analysis. Clinic Gastroenterol Hepatol 2019;17 1525–32.e1.
[22] Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. Gastroenterology 2018;155 337–46.e10.
[23] Privitera G, Pugliese D, Onali S, et al. Combination therapy in inflammatory bowel disease - from traditional immunosuppressors towards the new paradigm of dual targeted therapy. Autoimmun Rev 2021;20:102832.
[24] Chupin A, Perduca V, Meyer A, Bellanger C, Carbonnel F, Dong C. Systematic review with meta-analysis: comparative risk of lymphoma with anti-tumour necrosis factor agents and/or thiopurines in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2020;52:1289–97.
[25] Doherty G, Katsanos KH, Burisch J, et al. European Crohn's and colitis organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. J Crohns Colitis 2018;12:17–31.
[26] Noor NM, Sousa P, Bettenworth D, et al. ECCO topical review on biological treatment cycles in Crohn's disease. J Crohn's Colitis 2023.
[27] Ungar B, Levy I, Yavne Y, et al. Optimizing anti-TNF-α therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. Clinic Gastroenterol Hepatol 2016;14 550–7.e2.