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Alimentary Tract

Efficacy and safety of combination targeted therapies in immune-mediated inflammatory disease: the COMBIO study

Lucas Guillo[a,**,*], Benoit Flachaire[b,**], Jérôme Avouac[c], Catherine Dong[d], Maria Nachury[e], Guillaume Bouguen[f], Anthony Buisson[g], Ludovic Caillo[h], Mathurin Fumery[i], Cyrielle Gilletta[j], Xavier Hébuterne[k], Pierre Lafforgue[b], David Laharie[l], Emmanuel Mahé[m], Hubert Marotte[n], Stéphane Nancey[o], Sébastien Ottaviani[p], Jean-Hugues Salmon[q], Guillaume Savoye[r], Mélanie Serrero[a], Mathieu Uzzan[s], Manuelle Viguier[t], Christophe Richez[u], Laurent Peyrin-Biroulet[v], Philipe Seksik[w], Thao Pham[b], For the COMBIO Study Group[1]

[a] Aix Marseille Univ, APHM, University Hospital of Marseille Nord, Department of Gastroenterology, Marseille, France
[b] Aix Marseille Univ, APHM, University Hospital of Marseille Sainte-Marguerite, Department of Rheumatology, Marseille, France
[c] Université de Paris, service de rhumatologie, hôpital Cochin, AP-HP.CUP, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France
[d] Service de Gastro-Entérologie, Assistance publique-Hôpitaux de Paris (AP-HP), hôpital Bicêtre, 94270 Le Kremlin-Bicêtre, France
[e] Université de Lille, Inserm, CHU Lille, U1286 - INFINITE - Institute for Translational Research in Inflammation, F-59000 Lille, France
[f] CHU Rennes, Univ Rennes, INSERM, CIC1414, Institut NUMECAN (Nutrition Metabolisms and Cancer), 35000 Rennes, France
[g] Université Clermont Auvergne, 3iHP, CHU Clermont-Ferrand, Service d'Hépato-Gastroentérologie, Inserm U1071, M2iSH, USC-INRA 2018, Clermont-Ferrand, France
[h] Department of Gastroenterology, University Hospital of Nimes, Nimes, France
[i] Department of Gastroenterology, Amiens University Medical Center and PeriTox UMR I-O1, Jules Verne University of Picardie, Amiens, France
[j] Department of Gastroenterology, Toulouse University Hospital, Toulouse, France
[k] Gastroenterology and Clinical Nutrition, CHU of Nice, University Côte d'Azur, Nice, France
[l] CHU de Bordeaux, Hôpital Haut-Lévêque, Service d'Hépato-gastroentérologie et oncologie digestive – Université de Bordeaux, F-33000 Bordeaux, France
[m] Dermatology Department, Hôpital Victor Dupouy, Argenteuil, France. Groupe de recherche sur le Psoriasis (GrPso) de la Société Française de Dermatologie
[n] Department of Rheumatology, Inserm U1059-LBTO, CHU Saint-Etienne, Saint-Etienne, France
[o] Department of Gastroenterology, Inserm U1111-CIRI, Lyon-Sud University Hospital, Hospices Civils de Lyon, Pierre Bénite, France
[p] Departement of Rheumatology, DMU Locomotion, Hôpital Bichat-Claude Bernard, APHP, Université de Paris, Paris, France
[q] Department of Rheumatology and EA 3797, University of Reims Champagne-Ardenne, Reims, France
[r] Department of Gastroenterology, Rouen University Hospital, Rouen, France
[s] Department of Gastroenterology, IBD unit, Beaujon Hospital, APHP, Clichy, France
[t] Department of Dermatology-Venereology, Hôpital Robert Debré, Université Reims Champagne-Ardenne, Reims, France
[u] Rheumatology Department, CHU de Bordeaux, and ImmunoConcEpt, CNRS, UMR 5164, University of Bordeaux, Bordeaux, France
[v] Department of Gastroenterology and INSERM NGERE U1256, University Hospital of Nancy, University of Lorraine, Vandoeuvre-lès-Nancy, France
[w] Department of Gastroenterology, Centre de recherche Saint-Antoine, Sorbonne Université, INSERM, APHP, Hôpital Saint-Antoine, Paris, France

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ABSTRACT

Background: Use of a combination of targeted therapies (COMBIO) in patients with refractory/overlapping immune-mediated inflammatory diseases (IMIDs) has increased, but reported data remain scarce. We aimed to assess effectiveness and safety of COMBIO in patients with IMIDs.
Methods: We conducted a French ambispective multicenter cohort study from September 2020 to May 2021, including adults' patients with 1 or 2 IMIDs and treated at least 3-month with COMBIO.
Results: Overall, 143 patients were included. The most common IMIDs were Crohn's disease (63.6%), axial spondyloarthritis (37.7%), and ulcerative colitis (14%). Half of patients had only one IMID, of which 60% were Crohn's disease. Mean duration of COMBIO was 274.5±59.3 weeks, and COMBIO persistence at 104

* Corresponding author at: Department of Gastroenterology, University Hospital of Marseille Nord, University of Aix-Marseille, Chemin des Bourrely, 13015 Marseille, France.
E-mail address: lucas.guillo690@gmail.com (L. Guillo).
** Equal Contribution
[1] COMBIO Study Group.

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weeks was estimated at 64.1%. The most frequent COMBIOs combined anti-TNF agents with vedolizumab (30%) or ustekinumab (28.7%). Overall, 50% of patients achieved significant and 27% mild-to-moderate improvement in patient-reported outcomes. Extended duration of COMBIO (aOR=1.09; 95% CI: 1.03-1.14; p=0.002) and diagnoses of two IMIDs (aOR=3.46; 95%CI: 1.29-9.26; p=0.013) were associated with significant improvement in patient-reported outcomes. Incidence of serious infection during COMBIO was 4.51 per 100 person-years (95% CI 2.20-8.27) and 5 COMBIOs were discontinued due to adverse events.
Conclusions: COMBIO can be effective and safe in patients with refractory/overlapping IMIDs.

1. Introduction

The management of immune-mediated inflammatory diseases (IMIDs) has dramatically changed with the emergence of biologics and Janus kinase inhibitors (JAKi) [1,2]. Although these innovative treatments have expanded therapeutic options, a significant proportion of patients do not achieve remission; notabley, 45-60% of patients with axial spondyloarthritis [3–6], 10-60% with psoriasis [7–9], and 20-40% with inflammatory bowel disease (IBD) [10–13]. Combination therapies of anti-tumor necrosis factor (anti-TNF) agents and immunosuppressants are more efficient in rheumatological, gastroenterological, and dermatological inflammatory disorders, particularly in patients with insufficient improvement from traditional treatments [14–18]. Despite this wide range of available therapies, the effects of combined therapies remain to be elucidated. Moreover, patients may have multiple IMIDs, leading to complex clinical situations [19,20]. Combination of targeted therapy (COMBIO) may be a promising option in these challenging situations. While there are numerous case reports and case series on the use of COMBIO to treat patients with IMIDs. However, randomized control and open label studies are still scarce [21,22]. Although COMBIO appears to be an attractive treatment option, effectiveness and safety data remain limited, demonstrating a clear need for additional study and this lack of data limits its application in clinical practice [23]. Here, we report data from an ambispective, multicenter study to assess effectiveness and safety profile of COMBIO in clinical settings.

2. Methods

2.1. Study population and study design

We conducted a national, ambispective French cohort study on 143 patients with IMIDs treated with COMBIOs between September 2020 and May 2021. The study was performed in collaboration with French gastroenterologists, rheumatologists, and dermatologists from national expert groups of the GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif), the CRI (Club Rhumatismes et Inflammation) and the GRPso (Groupe de Recherche sur le Psoriasis de la Société Française de Dermatologie). Participating centers were tertiary centers for IBD, chronic inflammatory rheumatic disorders, or psoriasis. Case report forms were sent to physicians through the GETAID, CRI and GRPso mailing lists, reaching over 8,000 gastroenterologists, rheumatologists, internists, and dermatologists with a special interest in IMIDs. Inclusion criteria were as follows: age ≥18 years, with 1-2 IMIDs and currently receiving, or previously treated with a COMBIO comprised of two biologics, and/or targeted synthetic treatment. Patients were excluded if they had not completed at least 3 months of follow-up with their referring physician. In cases where the same patient was treated by two different specialists, only the first record was included in the study, and in cases where several COMBIO treatments were observed in the same patient, all COMBIOs were included in the analysis.

The study was conducted according to the French MR004 methodology of CNIL (Commission Nationale de l'Informatique et des Libertés) with the reference number 2210131 and submitted to the Health Data Hub according to the French regulation. Information on study objectives and rights to withdraw and opposition to the use of their data was sent to patients. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

2.2. Data Collection

The following data for each patient were collected: sex, date of birth, smoking status, body mass index (BMI), date and type of IMID(s) diagnosis, COMBIO (drugs, dosage, and start date of each drug), and any combination with an immunosuppressant. The reasons for discontinuation of COMBIO was documented as primary nonresponse, secondary loss of response, infection, remission, other. If no discontinuation occurred, the date of last visit was recorded.

We collected rates of infection, neoplastic events, deaths, and of any other adverse events during COMBIO. The severity of infections was classified as either mild-to-moderate infections for outpatient management, or serious infections leading to conventional hospitalization, admission to an intensive care unit (ICU) or death. As there is no common tool to simultaneously assess treatment response for gastroenterological, rheumatological and dermatological IMIDs, we used the Patient Global Impression of Change (PGIC) score [24] to evaluate the effectiveness of COMBIO, which is a validated tool for assessing clinically significant changes in patients.

2.3. Study Outcome Measures

The primary outcome was to assess the effectiveness and to assess short- and medium-term safety of COMBIO. The effectiveness of COMBIO was defined using the PGIC score. Patients were divided into three groups according to the PGIC score: (i) no-improvement (PGIC score from 1 to 2); (ii) mild-to-moderate improvement (PGIC score from 3 to 5); (iii) significant improvement (PGIC score from 6 to 7). To evaluate safety data, the incidence of serious infections was calculated and expressed as number of infections per 100 person-years (py).

The secondary outcomes were to identify characteristics of COMBIO in patients with IMIDs, identify factors associated with COMBIO effectiveness, and evaluate association between C-reactive protein (CRP) level and PGIC score. We also assessed which COMBIOs were employed most frequently, which IMIDs were the most common, the distribution of a single IMID versus overlapping IMIDs within the cohort, the follow-up duration, the time to the first COMBIO, the duration of COMBIO, and the reasons for discontinuation. Follow-up duration was defined as the time from diagnosis to the discontinuation of COMBIO, or the date of last visit if patients did not discontinue the COMBIO. Time to the first COMBIO was defined as the time from diagnosis to the start of the COMBIO, and duration of COMBIO was defined as the time from the start of COMBIO to the date of discontinuation, or the date of last

visit if patients did not discontinue the COMBIO. Potential factors associated with treatment response were analyzed: sex, number of IMIDs, age, duration of COMBIO, and type of treatment. These factors were chosen according to their clinical relevance in order to compare outcomes in patients with no improvement versus those with mild-to-moderate and significant improvement. Potential association between CRP level and PGIC score, was evaluated by comparing the proportion of patients who did not demonstrate CRP improvement compared to baseline, to those that achieved a normalized CRP (<5 mg/L), and those whose CRP improved relative to the median at the last observation carried forward (LOCF) at 3, 6 or 12 months.

2.4. Statistical Analysis

Categorical variables were described as percentage, while continuous variables were reported as mean ± standard deviation (SD), or median and interquartile range (IQR), depending on distribution. The duration of COMBIO was assessed with the Kaplan-Meier method. Data were censored at the date of COMBIO discontinuation, or the date of the last visit. A multinomial logistic regression was performed to obtain adjusted odds ratios (aOR) of the potential predicting factors. A Wilcoxon test was performed for the comparative analysis between baseline and LOCF CRP level. The comparative analysis of CRP level improvement according to the PGIC score was performed using Fisher's exact test.

3. Results

3.1. Patients and COMBIO characteristics

Overall, 150 COMBIOs in 143 patients with IMIDs were included in the study (Table 1). There were 87 women (60.8%) in the cohort, with a mean age of 42.1 years (±15.2). The characteristics of the cohort are presented in Table 1. The most frequent IMID was Crohn's disease (63.6%), followed by axial spondyloarthritis (37.7%), ulcerative colitis (14%), rheumatoid arthritis (9.1%), psoriatic arthritis (6.3%) and psoriasis (5.6%). Half of patients had a single disease (73/143, 51.0%), predominantly Crohn's disease (45/73, 61.6%). For these patients, 79 COMBIOs were collected. Seventy patients (49%) had two IMIDs, from which 71 COMBIOs were collected. The mean follow-up duration for the first or only disease was 16.4 years (± 9.8), and 7.4 years (± 6.2) for the second disease (for the 70 patients with two diseases). Among patients with two diseases, the average follow-up time between the two diseases was 8.6 years (± 7.9).

The distribution of treatments in the cohort are reported in Table 2 and all COMBIOs are listed in *e*Table 1. In 34 cases (22.7%), COMBIO was also combined with an immunosuppressant: methotrexate (22, 14.7%), azathioprine (9, 6%), leflunomide (2, 1.3%), sulfasalazine and leflunomide (1, 0.7%). The three most common COMBIOs were anti-TNF agents and vedolizumab (30%), anti-TNF agents and ustekinumab (28.7%), and vedolizumab and ustekinumab (8%). Among anti-TNF agents, the most common drugs were golimumab and adalimumab. The average time to the first COMBIO was 14.6 years (±9.8) in patients with one disease, and 5.7 years (±6.1) in patients with two diseases.

3.2. Efficacy of COMBIOs

Overall, the mean duration of COMBIO was 274.5 weeks (± 59.3). Survival without COMBIO discontinuation was estimated at 94.2%, 83.4%, 74.9% and 64.1%, at 12, 24, 52 and 104 weeks, respectively (Figure 1). COMBIO was stopped in 31.1% of cases (47/150), with 74.4% discontinuing due to primary nonresponse and/or secondary loss of response, and two (4.3%) discontinuations due to remission (Table 2).

Table 1
Patient characteristics.

	Patients (n=143)	SD
Female [n (%)]	87 (60.8)	
Age (years, mean)	42.1	15.2
Smokers [n (%)]	122†	
Active	20 (16.4)	
Former	31 (25.4)	
Non-smoker	71 (58.2)	
BMI (kg/m^2) [n (mean)]	126† (24.5)	5.3
All Diseases [n (%)]	213	
Crohn's disease	91 (63.6)	
Axial spondyloarthritis	54 (37.7)	
Ulcerative colitis	20 (14)	
Rheumatoid arthritis	13 (9.1)	
Psoriatic arthritis	9 (6.3)	
Psoriasis	8 (5.6)	
Other*	18 (12.6)	
Patient with one disease [n (%)]	73 (51)	
Crohn's disease	45 (61.6)	
Axial spondyloarthritis	3 (4.1)	
Ulcerative colitis	6 (8.2)	
Rheumatoid arthritis	7 (9.6)	
Psoriatic arthritis	4 (5.5)	
Psoriasis	0 (0)	
Other**	8 (11)	
Patients with two diseases [n (%)]	70 (49)	
Crohn's disease	46 (65.7)	
Axial spondyloarthritis	51 (72.9)	
Ulcerative colitis	14 (20)	
Rheumatoid arthritis	6 (8.6)	
Psoriatic arthritis	5 (71.4)	
Psoriasis	8 (11.4)	
Other**	10 (14.3)	
Follow-up duration (years) [n (mean)]		
One disease	141† (16.4)	9.8
Two diseases	68† (7.4)	6.2
Time between the two diseases	68† (8.6)	7.9
Crohn's disease	91 (15.0)	8.3
Axial spondyloarthritis	52† (10.0)	9.8
Ulcerative colitis	20 (11.0)	7.0
Rheumatoid arthritis	12† (17.8)	12.6
Psoriatic arthritis	8† (14.5)	7.7
Psoriasis	8 (12.0)	9.1

BMI, body mass index.
* juvenile idiopathic arthritis (n=4); connective tissue diseases (n=3); asthmas (n=3); acquired hyperostosis syndrome (n=1); atopic dermatitis (n=1); urticaria (n=1); Schnitzler syndrome (n=1); systemic sclerosis (n=1); interstitial lung disease (n=1); secondary amyloidosis (n=1); neuromyelitis optica (n=1).
** juvenile idiopathic arthritis (n=4); connective tissue diseases (n=2); acquired hyperostosis syndrome (n=1); systemic sclerosis (n=1).
† Missing data.

At the end of the follow-up, half of COMBIO (74/148, 50%) cases resulted in significant improvement in patient-reported outcomes, and 27% (40/148) of patients experienced mild-to-moderate improvement (Table 3). COMBIOs in patients with two diseases resulted in a numerically higher rate of significant improvement (PGIC 6 to 7) compared to patients with a single disease (57.1% vs 43.6%), whereas rates of mild-to-moderate improvement (PGIC 3 to 5) were similar (28.6% vs 25.6%). Treatment with immunosuppressants was similar across PGIC categories, with 27.8%, 36.1%, and 36.1% for PGIC 1-2, PGIC 3-5, and PGIC 6-7, respectively. Significant improvement was associated with the duration of COMBIO (aOR=1.09, 95% CI 1.03-1.14, p=0.002) and two concomitant diseases (aOR=3.46, 95% CI 1.29-9.26, p=0.013) (*eTable 2*). Age, sex, or treatment type were not associated with mild-to-moderate or significant improvement.

Data on CRP levels were available in 94 patients at baseline, and in 90 patients at 3, 6 and/or 12 months LOCF. At baseline, me-

Table 2
Characteristics of Treatments and COMBIOs.

	COMBIOs (n=150)	SD
Treatment distribution [n (%)]		
Anti-TNF	115 (76.7)	
Adalimumab	34 (22.7)	
Golimumab	31 (20.7)	
Infliximab	21 (14)	
Certolizumab	16 (10.7)	
Etanercept	13 (8.7)	
Vedolizumab	61 (40.7)	
Ustekinumab	58 (38.7)	
JAKi	23 (15.3)	
Tofacitinib	15 (10)	
Baricitinib	7 (4.7)	
Upadacitinib	1 (0.7)	
Rituximab	11 (7.3)	
Secukinumab	6 (4)	
Tocilizumab	6 (4)	
Other*	20 (13.3)	
Most frequent COMBIOs [n (%)]		
Anti-TNF + VDZ	45 (30)	
GOLI + VDZ	16 (10.7)	
ADA + VDZ	12 (8)	
IFX + VDZ	7 (4.7)	
CZP + VDZ	7 (4.7)	
ETN + VDZ	3 (2)	
VDZ + UST	12 (8)	
Anti-TNF + UST	43 (28.7)	
ADA + UST	15 (10)	
GOLI + UST	13 (8.7)	
IFX + UST	8 (5.3)	
CZP + UST	6 (4)	
ETN + UST	1 (0.7)	
Time to first COMBIO (years) [n (mean)]		
One disease	141† (14.6)	9.8
Two diseases	68† (5.7)	6.1
Crohn's disease	91 (13.5)	8.6
Axial spondyloarthritis	52† (8.4)	10
Ulcerative colitis	20 (9.1)	6.9
Rheumatoid arthritis	13 (14.9)	12.7
Psoriatic arthritis	8† (13.1)	7
Psoriasis	8 (10)	8.3
Duration of COMBIO (weeks) [n (mean)]	150 (274.5)	59.3
Association with immunosuppressants [n (%)]**	36 (24)	
Cause of COMBIO discontinuation [n (%)]	47 (31.3)	
Primary nonresponse (PNR)	16 (34)	
Secondary loss of response (LOR)	15 (31.9)	
PNR + LOR	4 (8.5)	
Infection	3 (6.4)	
Remission	2 (4.3)	
Other***	7 (14.9)	

ADA, adalimumab; CZP, certolizumab; COMBIO combination of targeted therapies; ETN, etanercept; GOLI, golimumab; IFX, infliximab; JAKi, Janus kinase inhibitor; TNF, tumor necrosis factor; UST, ustekinumab; VDZ, vedolizumab.

* abatacept (n=4); mepolizumab (n=2); denosumab (n=2); anakinra (n=2); brodalumab (n=1); risankizumab (n=1); dupilumab (n=1); canakinumab (n=1); sarilumab (n=1); guselkumab (n=1); apremilast (n=1); omalizumab (n=1); nintedanib (n=1); benralizumab (n=1);.

** methotrexate, thiopurines, leflunomide or sulfasalazine.

*** hypoglycemia (n=2), abdominal pain (n=1), loss of follow-up (n=1), weight gain (n=1), headache (n=1) and pregnancy plan (n=1).

† Missing data.

dian CRP was 23.3 mg/L [IQR 37;72], while LOCF CRP was 5.8 mg/L [IQR 2.2; 14.3], demonstrating a significant reduction in median CRP from baseline to LOCF (p<0.0001) (Table 4). Among 75 patients (79.8%) with a CRP ≥ 5 mg/L at baseline: 23 (30.7%) normalized CRP levels (< 5 mg/L), with 18 (24%) achieving PGIC 6-7 and 5 (6.7%) reaching PGIC 3-5. The normalization of CRP was significantly associated with the improvement of PGIC score (p=0.011). Compared to the median of the cohort, 47/94 (50%) patients had a CRP ≥ 23 mg/L (56 mg/L [IQR 37; 72]) at baseline (*eTable 3*). The normalization of CRP, compared to the median, was also significantly associated with an improved of PGIC score (p=0.005).

3.3. Safety of COMBIOs

Overall, 27 infections occurred during the 150 COMBIOs and 7 of which occurred for patients teaming up a COMBIO with an immunosuppressant (methotrexate (n=6), azathioprine (n=1)). Mild-to-moderate infections occurred in 12% (n=18) of cases and serious infections in 6% (n=9) of cases. Three serious infections were associated with methotrexate. The total exposure time was 199.75 patient years (py) and the estimated incidence of severe infection during COMBIO was 4.51 per 100py (95% CI 2.20-8.27). The occurrence of a serious infection led to the discontinuation of COMBIO in three patients: one *Clostridioides difficile* colitis (adalimumab and certolizumab), one *Pseudomonas aeruginosa* lung infection (tocilizumab, rituximab and methotrexate) and one hemophagocytic syndrome related to zoonosis (adalimumab and vedolizumab) (*eTable 4)*. The patient who experienced the *Pseudomonas aeruginosa* lung infection was admitted to the intensive care unit and died during care.

Ten non-infectious treatment-related adverse events were reported with COMBIOs (6.7%, Table 5). Only one patient experienced a neoplastic event (0.7%), developing a parotid gland acinic cell carcinoma during the period of treatment with the combination of adalimumab and denosumab.

4. Discussion

In our cohort, COMBIOs were used at similar frequencies for patients with one refractory IMID and those with two concurrent IMIDs. Of patients with a single IMID, 60% had Crohn's disease, which was the most common disease (63.6%) in the cohort. The second was axial spondyloarthritis (37.7%), but this diagnosis was predominantly associated with IBD, as only 3 patients were treated with a COMBIO solely for axial spondyloarthritis. This is in agreement with a previous retrospective cohort including 16 patients with IBD and extra-intestinal manifestations, where 11/16 patients had Crohn's disease, and 6/11 also had axial spondyloarthritis [25]. We found that the most common COMBIOs involved anti-TNF agents combined with ustekinumab or vedolizumab, which is consistent with a retrospective study in Crohn's disease patients [26]. A recent meta-analysis of 30 studies including 288 COMBIOs also reported the most frequent combinations were anti-TNF agents combined with vedolizumab, and ustekinumab combined with vedolizumab [27].

A previous publication reported 50% of patients with Crohn's disease reached clinical response, and 41% clinical remission [26]. In our study, 46.3% of patients with Crohn's disease achieved significant improvement by the end of the study. In the recent meta-analysis reporting 288 COMBIOs, 59% of patients achieved clinical remission [27]. However, this study included mainly refractory IBD (81%), and only 12% reported concurrent IMIDs. Thus, it is difficult to compare results, as our study population was heterogeneous, and although IBD patients were widely represented (77.6%), 54% were concurrent to other IMIDs. In a retrospective study including 14 patients with IBD and concurrent IMIDs [25], four reached remission for both diseases, and six reached remission, or mild activity, for both diseases; however, four patients were already in remission at baseline for their IBD or IMID. In our study, based on the PGIC score, half of patients achieved significant improvement, and a quarter had mild-to-moderate improvement. It is difficult to compare our results to previous reports, as the PGIC does not provide a specific disease activity metric for each IMID [24]. However, we demonstrated that PGIC score improvement was significantly associated with the normalization of CRP, emphasizing the relevancy of using this score to assess treatment response. We observed a significant improvement in median CRP from baseline to LOCF (p<0.0001), which is consistent with two other studies re-

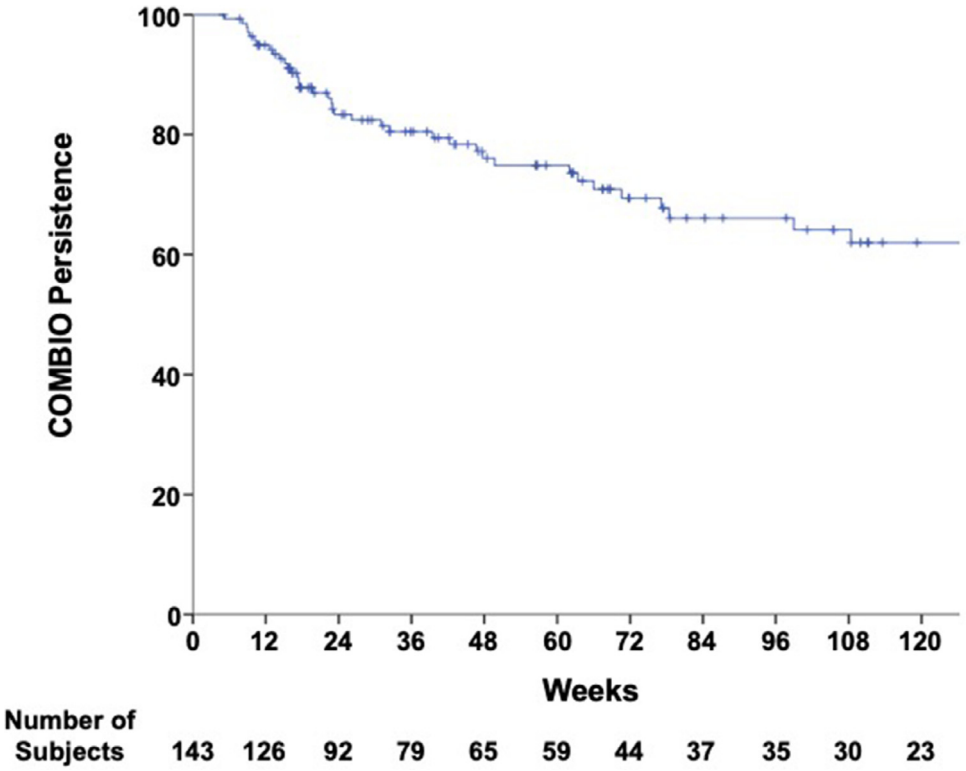

Figure 1. Survival Analysis based on Duration of COMBIO.

Table 3
Clinical improvement with a COMBIO according to the PGIC score.

	Total (n)	No Improvement (PGIC 1 to 2)	Mild-to-moderate Improvement (PGIC 3 to 5)	Significant Improvement (PGIC 6 to 7)
All COMBIOs [n (%)]	148†	34 (23)	40 (27)	74 (50)
Diseases [n (%)]				
Crohn's disease	95	21 (22.1)	30 (31.6)	44 (46.3)
Axial spondyloarthritis	55	6 (10.9)	16 (29.1)	33 (60)
Ulcerative colitis	21	6 (28.6)	3 (14.3)	12 (57.1)
Rheumatoid arthritis	13†	5 (38.5)	1 (7.7)	7 (53.8)
Psoriatic arthritis	9	3 (33.3)	1 (11.1)	5 (55.6)
Psoriasis	8	1 (12.5)	1 (12.5)	6 (75)
Other	17†	2 (11.8)	8 (47)	7 (41.2)
Number of Diseases [n (%)]				
One	78†	24 (30.8)	20 (25.6)	34 (43.6)
Two	70	10 (14.3)	20 (28.6)	40 (57.1)
Immunosuppressants [n (%)]	36	10 (27.8)	13 (36.1)	13 (36.1)
Treatments [n (%)]				
Anti-TNF	115	28 (24.3)	35 (30.5)	52 (45.2)
Vedolizumab	61	16 (26.2)	15 (24.6)	30 (49.2)
Ustekinumab	58	9 (15.5)	16 (27.6)	33 (56.9)
JAKi	22†	8 (36.4)	3 (13.6)	11 (50)
COMBIOs [n (%)]				
Anti-TNF/Vedolizumab	45	14 (31.1)	14 (31.1)	17 (37.8)
Golimumab/Vedolizumab	16	6 (37.5)	5 (31.3)	5 (31.3)
Adalimumab/Vedolizumab	12	3 (25)	5 (41.7)	4 (33.3)
Anti-TNF/Ustekinumab	42	6 (14.3)	15 (35.7)	21 (50)
Adalimumab/Ustekinumab	15	4 (26.7)	6 (40)	5 (33.3)
Golimumab/Ustekinumab	13	2 (15.4)	4 (30.8)	7 (53.8)
Vedolizumab/Ustekinumab	12	2 (16.7)	1 (8.3)	9 (75)

COMBIO combination of targeted therapies; JAKi, Janus kinase inhibitor; TNF, tumor necrosis factor.
† Missing data.

porting significant reductions of CRP post-treatment [25,26]. We also found that the COMBIO duration was associated with significant improvement in patient-reported outcomes, indicating that more COMBIO effectiveness results in longer treatment, with acceptable tolerability. Additionally, we demonstrated that the use of a COMBIO for two concomitant diseases was strongly associated with significant improvement, suggesting that COMBIO is more effective in overlapping IMIDs. Indeed, for single IMID, COMBIO was generally initiated in highly refractory disease, after the failure of multiple treatment lines.

Safety concerns are the main limitation for using COMBIO. Anti-TNF agents are associated with rates of serious infection that vary among diseases [28]. Data from several analyses reported that incidences per 100 py range from 3.4 to 6.7 in cases of IBD, 1.3 to

Table 4
CRP Normalization According to PGIC Score.

	Patients	Measurement (median mg/L)	[IQR] / p-value
All Patients			
Baseline CRP	94	23.3	[37; 72]
LOCF CRP[†]	90	5.8	[2.2; 14.3]
Patients with CRP ≥ 5 mg/L [n (%)]			
Initial CRP	75/94 (79.8)	36	[15.9; 64]
LOCF CRP[†]	75/90 (83.3)	7.6	[4; 23]
Normalization of CRP (< 5 mg/L) [n (%)]			0.011
PGIC 1 to 2	0/75 (0)		
PGIC 3 to 5	5/75 (6.7)		
PGIC 6 to 7	18/75 (24)		

CRP, C-reactive protein; LOCF, last observation carried forward; IQR, interquartile range.
[†] at 3, 6, 9 or 12 months after starting the COMBIO.

Table 5
Adverse Events.

	Events (n=150)
Infectious events [n (%)]	**27 (18)**
Mild-to-moderate infections	**18 (12)**
Rhinitis/sinusitis	4
Cutaneous infections[†]	4
Gastrointestinal infections[‡]	3
Vaginal mycosis	2
CMV	2
COVID-19	1
Lung infection	1
Conjunctivitis	1
Serious infections	**9 (6)**
Acute pyelonephritis	1
Clostridioides difficile infection	1
COVID-19	1
Herpes Zoster	1
Pseudomonas aeruginosa lung infection[±]	1
Catheter-related infection	1
Aspergillus sinusitis	1
Peri-appendicular abscess	1
Macrophage activation syndrome related to zoonosis	1
Adverse events [n (%)]	**10 (6.7)**
Hypoglycemia (rituximab and anti-TNF)	2
Weight gain >10 kg (anti-TNF)	2
Headache (anti-TNF)	2
Myoclonus (tofacitinib)	1
Abdominal pain post infusion (VDZ)	1
Skin xerosis (VDZ and CZP)	1
Axillary rash (ETN and baricitinib)	1
Neoplastic event [n (%)]	**1 (0.7)**
Parotid gland acinic cell adenocarcinoma (ADA and denosumab)	1

ADA, adalimumab; CZP, certolizumab; CMV, cytomegalovirus; COMBIO combination of biologics; ETN, etanercept; TNF, tumor necrosis factor; VDZ, vedolizumab.
[†] folliculitis (n=2), boil (n=1) and impetigo (staphylococcus) (n=1).
[‡] campylobacter jejuni (n=1) and perianal abscess (n=2).
[±] Death in intensive care unit.

1.4 in axial spondyloarthritis, and is 1.7 in psoriasis, 2.8 in psoriatic arthritis, and 4.6 in rheumatoid arthritis [29–31]. In addition, the risk of serious infection during treatment with a combination of anti-TNF agents and an immunosuppressant is increased in IBD patients [31,32], and a meta-analysis of 15 studies reported a 20% increase in serious infection compared to monotherapy [32]. It is well known that the risk of infection is lower for vedolizumab and ustekinumab as compared to anti-TNF agents, and generally no different from placebo [31]. In IBD, the incidence of serious infection is of 4.0 per 100py, and 3.4 and 4.3 per 100py for ustekinumab and vedolizumab, respectively [31,33,34]. In comparison, the incidence rate with ustekinumab is 0.74 for psoriatic arthritis, and 1.5 for psoriasis [31,35]. Finally, data for tofacitinib indicated an incidence rate of 2.4 in rheumatoid arthritis and 2.0 in ulcerative colitis [31]. During COMBIOs, we reported an rate of serious infection of 4.51 per 100py. This incidence rate is not increased compared to monotherapy of biologics, and especially compared to data with anti-TNF agents. Notably, one quarter of COMBIOs were associated with an immunosuppressant in our study, though we did not collect data on other risk factors for infection, such as comorbidities or corticosteroid therapy. The mean duration of COMBIO was less than 6 years in our study (274.5 weeks ± 59.3), and the total exposure time was 199.75 py. Thus, our study cannot report long-term safety data, but provides important data on short- and medium-term safety. Additionally, we report reasons for COMBIO discontinuation, which occurred in less than one third of cases. Only three patients discontinued COMBIO due to infections, and although eight adverse events (5.3%) occurred during follow-up, only two required discontinuation of COMBIO treatment. Only one patient experienced a neoplastic event (parotid gland acinic cell adenocarcinoma) during a COMBIO of adalimumab and denosumab. Discontinuation of COMBIO was primarily related to primary non-response and/or secondary loss of response (74.4%). Overall, safety data appears to be reassuring and comparable to monotherapy, which is also supported by available current literature [27,36].

This is the largest multicenter cohort study, and the first multidisciplinary initiative examining COMBIO effectiveness and safety. However, although it was an ambispective cohort, the study design and the heterogeneity of diseases did not allow us to collect other biomarkers and disease activity scores. Longer study follow-ups will be necessary to draw definitive conclusions about the use of COMBIO compared to monotherapy or classical combination therapy.

In conclusion, our study showed that COMBIO appears to be effective in achieving significant and mild-to-moderate improvement in half and a quarter of patients with IMIDs, respectively. The overall safety profile is acceptable, and comparable to monotherapy in the short- and medium-term. COMBIO can be a therapeutic option for medically refractory patients, and for patients with overlapping IMIDs. Prospective studies are needed to validate this approach, along with long-term safety studies.

Declaration of Competing Interest

L Guillo declares consulting fees for Abbvie. J Avouac has received consultancy relationship and/or received honoraria and/or participated to advisory boards from Galapagos, Lilly, Pfizer, Abbvie, Bristol-Myers Squibb, Sanofi, Roche-Chugai, Nordic Pharma, Medac, Novartis, Biogen, Fresenius Kabi, Janssen, and MSD. M Nachury received board membership, consultancy, or lecture fees from Abbvie, Adacyte, Amgen, Arena, Biogen, CTMA, Celltrion, Ferring, Fresenius-Kabi, Janssen, Mayoli-Spindler, MSD, Pfizer, Takeda. G Bouguen has served as a speaker, consultant or advisory board member abbvie, takeda, fresinus Kabin, Janssen, Vifor pharma, Sandoz, MSD, Biogen, TIllots, FErring, Amgen, Mylan. A Buisson de-

clares consulting fees for Abbvie, Amgen, Arena, Biogen, CTMA, Janssen, MSD, Pfizer, Roche, Takeda and Tillots. Lecture fees for Abbvie, Amgen, Biogen, Janssen, Mayoly-Spindler, MSD, Norgine Pfizer, Roche, Takeda and Tillots. L Caillo declares lecture and consulting fees for Abbvie, Pfizer, Ferring, Janssen, Amgen, Biogen, Takeda and Tillotts.

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Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

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Supplementary materials

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