Manuscript Doi: 10.1093/ecco-jcc/jjaa149

Dual Targeted Therapy: a possible option for the management of refractory Inflammatory Bowel Disease

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Non-standard abbreviations:

DTT: Dual Targeted Therapy

EIM: Extraintestinal manifestations

Manuscript Doi: 10.1093/ecco-jcc/jjaa149

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Conference presentation:

This work has never been presented to any conference.

Manuscript Doi: 10.1093/ecco-jcc/jjaa149

AUTHORS CONTRIBUTIONS

Giuseppe Privitera designed the study, contributed to data collection, performed statistical analysis and wrote the manuscript.

Sara Onali and Daniela Pugliese also contributed to write the manuscript and supervised data collection.

Sara Renna, Edoardo Savarino, Anna Viola, Davide Giuseppe Ribaldone, Andrea Buda, Cristina Bezzio, Gionata Fiorino, Silvio Danese, Massimo Claudio Fantini, Luisa Guidi, Franco Scaldaferri, Antonio Gasbarrini and Ambrogio Orlando contributed to data collection.

Alessandro Armuzzi oversaw the project, including statistical analysis and manuscript writing, and guarantees for the integrity of the work.

All authors reviewed and approved the final draft of the article before submission.

Manuscript Doi: 10.1093/ecco-jcc/jjaa149

ABSTRACT

Background and aims

Dual Targeted Therapy (DTT) has been proposed as a novel therapeutic strategy for the management of complicated patients with Inflammatory Bowel Diseases (IBD). Our aim was to investigate the safety and effectiveness of this approach in a real-life setting.

Methods

We retrospectively extracted data from IBD patients receiving DTT in Italian IBD referral centres. Baseline characteristics, clinical activity of intestinal and extraintestinal disease and C-reactive proteins levels were recorded. All adverse events were reported. Clinical effectiveness, biochemical remission and safety of DTT were investigated.

Results

Sixteen patients were identified; indications for DTT were: “active IBD” or “active EIM” despite ongoing biological therapy. The most commonly used DTT were: vedolizumab + ustekinumab (3 patients) and vedolizumab + adalimumab (3 patients). Clinical response of intestinal or extraintestinal symptoms, according to the indication for DTT, was reported by all patients by the end of the induction. Four patients discontinued DTT during follow-up. Three patients experienced an adverse event; no serious adverse event was reported.

Conclusions

DTT seems to be an effective and safe treatment and may represent an appealing therapeutic strategy for the management of complicated IBD patients.

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KEYWORDS

Combination Therapy

Extraintestinal manifestations

Biologics

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INTRODUCTION

Inflammatory Bowel Diseases (IBD) are systemic, progressive and disabling conditions[1]. Current available treatments and strategies do not guarantee an adequate control over intestinal symptoms, nor are able to induce deep remission, in each patient[2,3]; furthermore, up to 50% of IBD patients present with extraintestinal manifestations (EIM)[4] that may not be fully controlled despite ongoing IBD treatment.

Dual Targeted Therapy (DTT) might represent a promising strategy for the management of such complicated patients. However, few data on its effectiveness and safety exist to date [5].

We report the cases of IBD patients receiving DTT in Italian referral centres. All targeted therapies with immunomodulatory activity were included, both biologics and small molecules. Indication for DTT could be either: 1) "uncontrolled active IBD" in patients with or without EIM or 2) "active EIM" despite ongoing IBD therapy.

CASE REPORT

Starting from February 2017, 16 patients receiving DTT in 9 Italian IBD referral centres were identified. Patients' characteristics are summarized in table 1. Fourteen patients had IBD + concomitant EIM. Median age was 38 years (range 27-69) and median duration of IBD was 10.8 years (range 0.2-21.4).

The most frequently used drug was vedolizumab (12 patients, 75%), followed by anti-Tumor Necrosis Factor (TNF)-α agents (10, 62.5%) and ustekinumab (7, 43.8%); the most common combinations were: vedolizumab + ustekinumab (3 patients, 18.8%) and adalimumab + vedolizumab (3, 18.8%) (table 2).

Seven patients started DTT due to ongoing intestinal symptoms (table 2, group 1, patients 1-7), while the remaining 9 for uncontrolled EIM (table 2, group 2, patients 8-16). Patients 1 and 2 with Crohn's Disease had failed multiple biologics and undergone extensive bowel resections: in patient 1, a second agent was added (sequential induction), while in patient 2 a trial with a concomitant re-induction was given. Vedolizumab was added in three patients already on biological therapy for psoriatic disease (patients 3, 5

and 7) or rheumatoid arthritis (patient 4). Conversely, patients 8-14 were started with vedolizumab and subsequently needed DTT to treat EIM an anti-TNF agent was added in case of active Spondylarthritis (SpA) (patients 8 and 12-16), whereas, in the case of active psoriatic disease, other agents were chosen (patients 9-11). Finally, for both patients 15 and 16 on ustekinumab therapy, anti-TNF drugs were reintroduced to control SpA. All patients who started DTT for uncontrolled IBD had previously received therapy optimization (i.e.: dose escalation), besides patient 2 who started both drugs at the same time and patient 5 was on therapy with secukinumab. Three patients who started DTT due to uncontrolled EIM had previously received therapy optimization to treat IBD symptoms; in the remaining patients vedolizumab optimization for uncontrolled EIM or ustekinumab optimization for uncontrolled axial SpA were not considered appropriate and were not done, accordingly.

Median time on DTT was 7 months (range 3-28 months). Patients' assessments during follow-up are reported in table 3. Clinical improvement of intestinal (group 1) and extraintestinal (group 2) symptoms was reported by all patients at the end of the induction already. Notably, 3 patients in group 2 had also moderately active IBD when starting DTT for active EIM, and 2 of them showed an improvement in intestinal symptoms by the end of DTT induction. Eleven patients were on DTT for at least six months, 4 were still on therapy but had not reached six months yet and 1 discontinued DTT earlier (patient 14, group 2). At 6 months, clinical response and remission in intestinal symptoms (group 1) was reported by 3/7 (42.8%) and 1/7 (14.2%) patients in group 1, while clinical response and remission in extraintestinal symptoms was reported by 2/9 (22%) and 5/9 patients (55.5%) in group 2. C-reactive protein (CRP) normalization was recorded in 5 patients of 9 with high baseline serum levels (table 3). Among 8 patients on oral steroids at baseline, 6 (75%) were able to withdraw them after DTT introduction (table 3) without need of resuming. Four patients (25%) discontinued DTT for the following reasons: treatment failure (patients 13 and 15), clinical remission (patient 14, maintained with only one biological therapy) and loss to follow-up (patient 8, after a skin reaction).

Three patients (18.8%) experienced at least one adverse event (table 2). One patient had a cutaneous reaction following certolizumab administration, which led to drug discontinuation. Another patient was diagnosed with Drug-Induced Liver Injury (DILI), possibly secondary to apremilast, recovered after the

reduction of the dose. Finally, one patient, with history of perianal CD, developed a perianal abscess, managed with surgical drainage and seton placement. No serious AE were reported while on DTT.

DISCUSSION

In IBD patients, two archetypical scenarios which could require DTT can present. 1) "Uncontrolled IBD" in complicated patients (refractory IBD), where alternative therapeutic strategies are lacking and experimental drugs are not a viable option 2) "double indication" in patients with both IBD and EIM, where at least one of the two component is active despite ongoing therapy and out-of-class switch might not be advisable. Combination of therapeutical agents is currently used in IBD patients, especially in regards of corticosteroids and immunomodulators (thiopurines, methotrexate) with good efficacy profile[6], whereas combination of 2 biologics or one biologic and one small molecule remains still not widely considered in clinical practice because of the high costs and some concerns on the risks of serious adverse events.

In our cohort, DTT improved both intestinal and extra-intestinal symptoms in the majority of patients without significant safety issues. Moreover, after induction we recorded a drop of CRP serum levels to normal value in about half of patients, and steroids discontinuation in 6 of 8 patients who were on concomitant steroids at baseline.

The largest experiences with IBD patients starting DTT due to uncontrolled intestinal disease come from four recent studies that showed promising results. Interestingly, 8 out of 10 patients in the Buer's cohort were able to discontinue anti-TNFα treatment and continued vedolizumab alone as maintenance therapy[7–10]. Similarly, in our cohort, patient 14 discontinued DTT after achieving remission and continued monotherapy with a single agent as maintenance therapy. Therefore, DTT could be potentially used as a bridge therapy to induce remission, followed by maintenance therapy with only one drug.

One patient in our cohort (patient 5) experienced a reactivation of pouchitis after secukinumab induction and a partial improvement was observed after the introduction of vedolizumab. As previously reported, IL17 inhibition can be associated with new onset and relapse of IBD[11]: in such cases, gut-selective

agents, like vedolizumab, might represent a possible strategy to overcome these potential deleterious effects.

IBD are not characterized by a significant increase in mortality[12], so the possible benefits of DTT need to be carefully weighed in terms of cost-effectiveness and safety. In our cohort, no opportunistic nor serious infections were recorded and no malignancies were diagnosed. Our observations are in line with other experiences in IBD patients[13]. However, the short duration of follow-up might underestimate the occurrence of some adverse events that usually occur on the long term. Furthermore, most of our patients received anti-integrin treatment, that is usually associated with a favourable safety profile. Indeed, some concerns regarding DTT safety in rheumatological patients (mostly treated with anti-TNF plus anakinra, rituximab or abatacept) were raised: a trend towards increased rates of serious adverse events causing discontinuation was often observed and, in some cases, a higher number of malignancies was reported[5]. Finally, no evaluation on the cost-effectiveness of DTT was possible, and it needs further investigation.

Based on our data and in line with previous reports, we may propose a flow-chart summarizing the decision-making process to adopt DTT (figure 1). In the presence of active intestinal disease, with ongoing treatment bringing partial, but insufficient clinical benefit and no alternative options feasible, a second agent can be added (sequential induction); in the case of a patient already exposed to all licensed drugs, when surgery and/or inclusion in clinical trials are not a viable option, a double concomitant induction can be attempted. When, despite ongoing effective therapy on IBD, EIM are still active, the involved site needs to be considered: in the case of active SpA, an anti-TNF agent is preferred; in the remaining cases, another agent can be added. Finally, in the case of active intestinal disease with controlled extraintestinal manifestations, initiation of a gut-selective agent seems to be the safer and best option.

The main limitations of our study are The retrospective design, the small sample size, the short median follow-up, the heterogeneity of treatments, the impossibility to stratify patients according to the reasons for previous treatment failures and the lack of information on serum drug and anti-drug antibody levels. Nonetheless, it provides real-life examples of different clinical scenarios of IBD patients requiring DTT and proposes a practical approach for their management. DTT appears to be a ductile and reasonably safe strategy, that can be considered as an alternative strategy in the management of complex refractory cases.

Manuscript Doi: 10.1093/ecco-jcc/jjaa149

FUNDING

This work was not supported by any financial contribution.

AKNOWLEDGMENTS

None.

Conflicts of interest

The authors declare the following conflicts of interest: Giuseppe Privitera received consultancies fee from Alphasigma. Sara Onali received speaker fees from: Abbvie, Takeda, Amgen and Norgine. Daniela Pugliese received speaker fees from AbbVie, MSD, Takeda and Janssen, Pfeizer. Sara Renna served as an advisory board member for Abbvie and MSD Pharmaceuticals, and received lecture grants from Abbvie, Janssen, MSD and Takeda Pharmaceuticals. Edoardo Savarino received lecture and/or consultancies fees from: Abbvie, Amgen, Bristol-Myers Squibb, MSD, Janssen, Takeda, Sandoz, Frasenius Kabi. Davide Giuseppe Ribaldone received consultancies and/or speaker fees from: Janssen, Ferring, Errekappa. Andrea Buda received advisory board fees from Janssen and MSD and lecture fees drom Takeda. Gionata Fiorino served as a consultant and a member of Advisory Boards for MSD, Takeda Pharmaceuticals, AbbVie, Pfizer, Celltrion, Amgen, Sandoz, Samsung, and Janssen Pharmaceuticals. Luisa Guidi: consultancies and/or speaker fees from: AbbVie, Janssen, MSD, Mundipharma, Takeda, Vifor Pharma, Zambon. Silvio Danese received consulting fees from AbbVie, Allergan, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Gilead, Hospira, Janssen, Johnson & Johnson, MSD, Mundipharma, Pfizer, Roche, Sandoz, Takeda, TiGenix, UCB, and Vifor, and advisory board fees from Arena. Antonio Gasbarrini reports personal fees for consultancy for Eisai S.r.l., 3PSolutions, Real Time Meeting, Fondazione Istituto Danone, Sinergie S.r.l. Board MRGE, and Sanofi S.p.A, personal fees for acting as a speaker for Takeda S.p.A, AbbVie, and Sandoz S.p.A, and personal fees for acting on advisory boards for VSL3 and Eisai. Ambrogio Orlando served as an advisory board member for Abbvie, MSD, Janssen, Pfizer, Takeda Pharmaceuticals and

received lecture grants from Abbvie, MSD, Janssen, Sofar, Chiesi, Pfizer and Takeda Pharmaceuticals. Alessandro Armuzzi: consulting and/or advisory board fees from AbbVie, Allergan, Amgen, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Janssen, Lilly, MSD, Mylan, Pfizer, Samsung Bioepis, Sandoz, Takeda; lecture and/or speaker bureau fees from AbbVie, Amgen, Biogen, Ferring, Janssen, MSD, Mitsubishi-Tanabe, Nikkiso, Pfizer, Sandoz, Samsung Bioepis, Takeda; and research grants from MSD, Pfizer, Takeda. All the other authors have no conflict of interest to declare.

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Manuscript Doi: 10.1093/ecco-jcc/jjaa149

TABLE 1. Patients' baseline characteristics.

	Gender	Age (years)	Disease	Duration of disease (year)	Montreal	Previous therapies
1	M	29	CD	15.7	A1L1B2	IFX, ADA, VDZ, AZA
2	M	29	CD	5.7	A1L3B3p	IFX, ADA, VDZ, UST, AZA
3	F	31	CD	0.2	A2L2B1	IFX, ADA, ETN
4	F	49	UC	8.6	E2	IFX, ETA, AZA, MTX
5	F	43	UC	21.4	Pouchitis	IFX, ADA, GOL, CRZ, UST, AZA, apheresis
6	M	37	CD	20.4	A1L3B3	ADA
7	F	39	CD	4	A2L3B1	ADA, UST, CRZ, GOL, ETN
8	F	27	UC	3.7	A2E3	IFX, ADA, GOL, AZA
9	M	50	UC	24	A2E3	IFX, ADA, GOL
10	M	35	CD	21.3	A2L2B1	ADA, AZA, cyclosporine, apheresis
11	M	69	UC	7.7	E3	IFX
12	F	34	CD	7	A2L3B1	IFX, ADA
13	M	58	CD	10.7	A2L3B2p	IFX, AZA, MTX, ADA
14	F	39	CD	10.8	A2L2B1	IFX, ADA
15	F	57	CD	15.9	A2L3B1	IFX, AZA, MTX, ADA, VDZ, Mongersen
16	F	31	CD	20	A1L3B1	AZA, MTX, IFX

M: Male; F: Female; CD: Crohn's Disease; UC: Ulcerative Colitis; RA: Rheumatoid Arthritis; PsA: Psoriatic Arthritis; SpA: Spondyloarthritis; PSC: Primary Sclerosing Colangitis; QFT: Quantiferon-test; CVD: Cardiovascular disease; HCV: Hepatitis C Virus; IFX: Infliximab, ADA: Adalimumab; VDZ: Vedolizumab; UST: Ustekinumab; AZA: Azathioprine; ETN: Etanercpet; MTX: Methotrexate; GOL: Golimumab; CRZ: Certolizumab

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TABLE 2. Dual Targeted Therapy (DTT).

Patient	Indication for therapy 1	Therapy 1 (maintenance dose)	Indication for therapy 2	Therapy 2 (maintenance dose)	Duration of DTT	Still on DTT	Adverse events
Group 1 – Active IBD							
1	CD	UST (90 mg e8w)	CD	CRZ (200 mg e4w)	4 months	Y	Perianals abscess
2	CD	VDZ (300 mg e8w)	CD	UST (90 mg e12w)	5 months	Y	None
3	Pso	UST (90 mg e8w)	CD	VDZ (300 mg e8w)	8 months	Y	None
4	AR	ADA (40 mg ew)	UC	VDZ (300 mg e4w)	28 months	Y	None
5	Pso	SKM (300 mg e4w)	Pouchitis	VDZ (300 mg e8w)	7 months	Y	None
6	Pso	UST (90 mg e8w)	CD	IFX (5 mg/kg e8w)	6 months	Y	None
7	Pso	IFX (10 mg/kg e8w)	CD	VDZ (300 mg e8w)	2 months	Y	None
Group 2b – Active EIM							
8	UC	VDZ (300 mg e8w)	SpA	CRZ (200 mg e4w)	8 months	N	Cutaneous reaction
9	UC	VDZ (300 mg e8w)	Pso	UST (90 mg e8w)	12 months	Y	None
10	CD	VDZ (300 mg e8w)	Pso	APR (30 mg bid[1])	19 months	Y	DILI
11	UC	VDZ (300 mg e8w)	Pso	SKM (300 mg e4w)	5 months	Y	None
12	CD	VDZ (300 mg e8w)	SpA	CRZ (200 mg e4w)	6 months	Y	None
13	CD	VDZ (300 mg e8w)	SpA	ADA (40 mg ew)	10 months	N	None
14	CD	VDZ (300 mg e8w)	SpA	ADA (40 mg eow)	5 months	N	None
15	CD	UST (90 mg e12 w)	SpA	ADA (40 mg ew)	10 months	N	None
16	CD	UST (90 mg e12w)	SpA	IFX (5 mg/kg e8w)	6 months	Y	None

[1] Reduced after adverse event.

CD: Crohn's Disease; UC: Ulcerative Colitis; Pso: Psoriatic Disease; RA: Rheumatoid Arthritis; VDZ: Vedolizumab; UST: Ustekinumab; ADA: Adalimumab; CRZ: Certolizumab; APR: Apremilast; SKM: Secukinumab; IFX: Infliximab; ew: every week; eow: every other week; e4w: every 4 weeks; e8w: every 8 weeks; e12w: every 12 weeks; bid: twice daily; Y: Yes; N: No; DILI: Drug-Induced Liver Injury.

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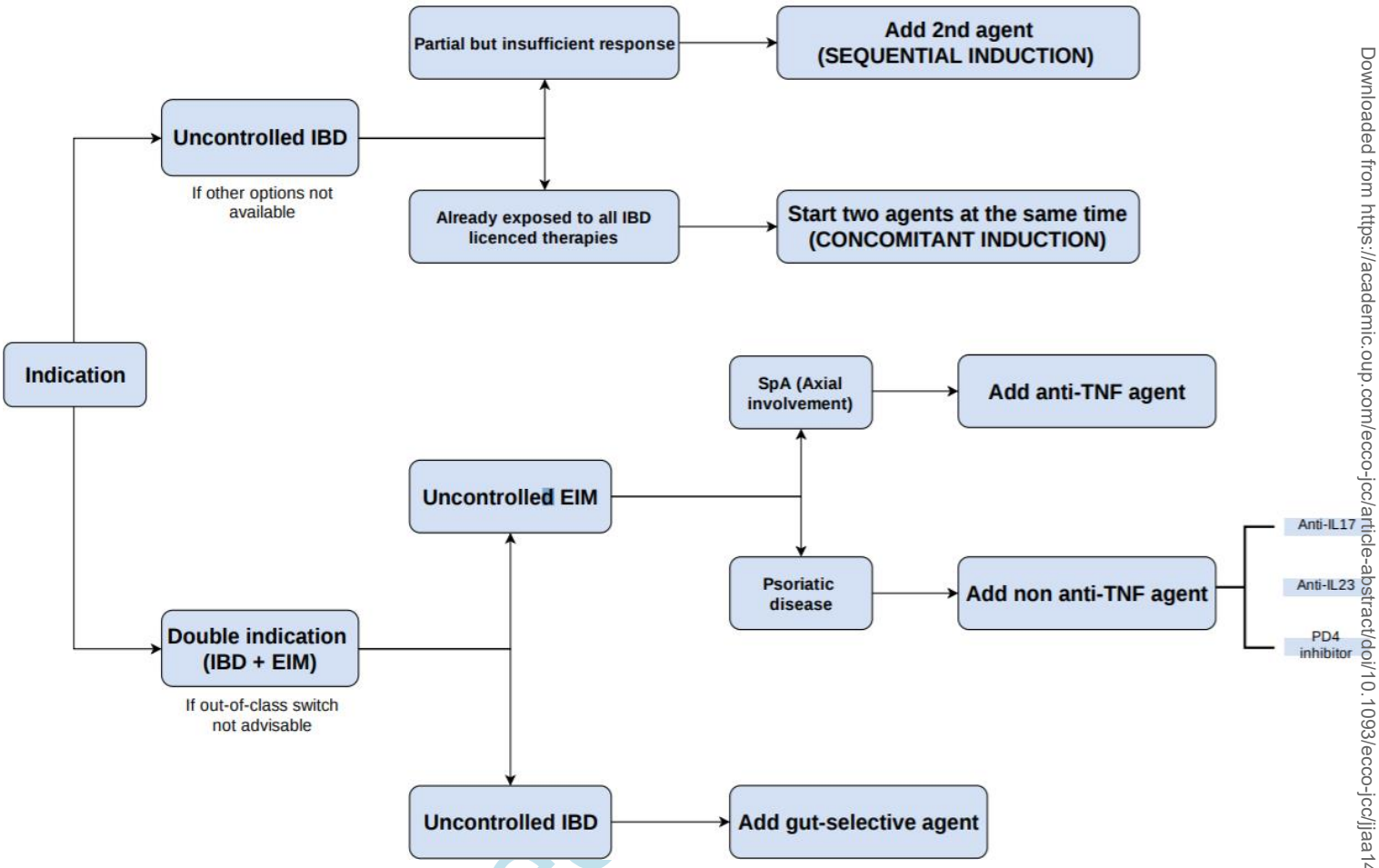
TABLE 3. Patients' assessment during follow-up

	Baseline				2 months				6 months		
Patient - DTT	**Clinical activity – intestinal**	**Clinical activity – EIM**	**CRP**	**Steroid therapy**	**Clinical activity – intestinal**	**Clinical activity – EIM**	**CRP**	**Steroid therapy**	**Clinical activity - intestinal**	**Clinical activity – EIM**	**CRP**
Group 1 – Active IBD											
1 - UST+CRZ	Moderate	NA	+	Y	Mild	NA	-	N	NA	NA	NA
2 - VDZ+UST	Moderate	NA	+	Y	Mild	NA	+	N	NA	NA	NA
3 - UST+VDZ	Moderate	Mild	+	N	Mild	Mild	+	N	Mild	Remission	-
4 - ADA+VDZ	Severe	Remission	-	Y	Mild	Remission	-	Y	Mild	Remission	-
5 - SKM+VDZ	Severe	Mild	+	Y	Moderate	Mild	+	N	Mild	Mild	+
6 - UST+IFX	Moderate	Remission	+	N	Remission	Remission	-	N	Remission	Remission	-
7 - IFX+VDZ	Moderate	Remission	+	Y	Mild	Remission	-	N	NA	NA	NA
Group 2b – Active EIM											
8 - VDZ+CRZ	Remission	Severe	-	N	Mild	Mild	-	N	Mild	Remission	+
9 - VDZ+UST	Moderate	Severe	-	Y	Mild	Mild	-	N	Mild	Remission	-
10 - VDZ+APR	Moderate	Severe	+	Y	Moderate	Mild	+	Y	Remission	Mild	+
11 - VDZ+SKM	Mild	Severe	+	N	Mild	Mild	-	N	NA	NA	NA
12 - VDZ+CZR	Remission	Severe	+	N	Remission	Remission	-	N	Remission	Remission	-
13 - VDZ+ADA	Mild	Severe	+	N	Remission	Mild	-	N	Remission	Remission	-
14 - VDZ+ADA	Mild	Severe	+	N	Remission	Remission	-	N	NA	NA	NA
15 - UST+ADA	Moderate	Severe	+	Y	Remission	Mild	-	N	Remission	Mild	-
16 - UST+IFX	Remission	Severe	+	N	Remission	Remission	+	N	Remission	Remission	-

Clinical activity of intestinal symptoms was categorized according to Harvey Bradshaw Index and partial Mayo Score for Crohn's disease and ulcerative colitis, respectively. EIM clinical activity was classified as severe, mild or remission according to clinical judgement. VDZ: Vedolizumab; UST: Ustekinumab; ADA: Adalimumab; CRZ: Certolizumab; APR: Apremilast; SKM: Secukinumab; IFX: Infliximab; + : positive; - : negative; Y: Yes, N: No; NA: not applicable.

Figure 1. Dual Targeted Therapy flow-chart



IBD: Inflammatory Bowel Disease; EIM: Extraintestinal Manifestations; SpA: Spondylarthritis; TNF: Tumor-Necrosis Factor; IL: Interleukin; PD4: phosphodiesterase 4