Real world evidence on the effectiveness and safety of tofacitinib in ulcerative colitis in Lebanon

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Abstract

Objective To evaluate the effectiveness and safety of tofacitinib in patients with ulcerative colitis (UC) in clinical practice in Lebanon.

Design This was a retrospective cross-sectional study. The data were collected from hospital records. Patients with moderate to severe UC treated with tofacitinib between 2018 and 2021 were included. Patients' demographics, disease-specific characteristics, clinical assessment at three time points (8, 26, and 52 weeks), endoscopic evaluation at 24 weeks, and adverse events were collected.

Results A total of 60 UC patients with a mean duration of disease of 7.9 ± 4.7 years were enrolled. 61.7% of patients had extensive disease, and 58.3% had received ≥ 1 biologic prior to tofacitinib. Clinical remission was reported in 25, 34, and 31 patients (41.7%, 56.7%, and 56.4%) at 8, 26, and 52 weeks respectively. Endoscopic remission (endoscopic Mayo score 0 or 1) was observed in 58.3% of patients at 52 weeks. About one-third of patients (31.7%) stopped tofacitinib at one year, primarily for lack of efficacy or loss of response, with no significant difference between biologics-naïve and experienced patients (24% vs. 37.1% respectively). No serious adverse events or deaths were reported. Adverse events were reported in 3 patients (5.0%) - one *C. difficile* infection, one case of reversible lymphopenia, and one case of facial acne. No serious adverse events or deaths were noted. On multivariate analysis, biologic-naïve status and reduction or normalization of CRP were associated with clinical remission (OR = 10.87, 95% CI = 1.57, 100, and OR = 78.47, 95% CI = 2.09, 2940.32 respectively), while reduction or normalization of CRP was associated with endoscopic remission at 1 year (OR = 19.03, 95% CI = 1.64, 221.09).

Conclusion Tofacitinib was effective in the treatment of moderately severe ulcerative colitis in this real-world cohort in Lebanon. Further, the predictors associated with clinical and endoscopic remissions were found to be biologic-naïve status and reduction in CRP. Observed AEs were consistent with the known safety profile. One of the major limitations of this study is the smaller sample size and the retrospective nature of the study.

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Key Message

What is already known on this topic – Although effectiveness of tofacitinib in ulcerative colitis has been established via real world evidence studies (RWDs), there have been no reports of RWD in West Asia or the Middle East and North Africa (MENA) region.

What this study adds – It was observed that biologic-naïve status of patients and reduction in C-reactive protein (CRP) levels were associated with clinical and endoscopic remission outcomes. Tofacitinib was effective in the treatment of moderately severe UC in the Lebanese real-world cohort and observed AEs were consistent with the known safety profile.

How this study might affect research, practice, or policy – This study provides insights to the physicians managing UC patients in the MENA region on the expected clinical journey for patients being treated with tofacitinib as well as the predictors of outcome. Future comparisons of this study with similar RWE studies in different geographical locations, will delineate the differences, if any, in the clinical course, based on demographic factors.

Keywords Persistence, Janus kinase inhibition, Inflammatory bowel disease

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with a relapsing-remitting pattern that causes an increased frequency of bowel movements and bloody diarrhea, leading to organ damage and impaired quality of life [1]. The primary goals of therapy in ulcerative colitis (UC) are reducing mucosal inflammation and maintaining symptom remission, though these aims are not achieved in all patients.[1] Despite the array of medical options available, treatment failure is common and refractory disease represents an unmet clinical need.[2] Hence, additional treatments including those with different new modes/mechanisms of actions are needed. The efficacy and safety profile of tofacitinib, an inhibitor of the Janus Kinase (JAK) family of kinases and a first in class oral small molecule, has been demonstrated as induction and maintenance therapy in three pivotal randomized, placebo-controlled trials in patients with moderate to severe ulcerative colitis [2]. Real world data (RWD) has become increasingly important in providing additional evidence of treatment effectiveness in clinical practice. A number of RWD and a systemic review and meta-analysis on RWD have been reported confirming the effectiveness of tofacitinib in ulcerative colitis in clinical practice [1, 3–7]. However, there have been no reports of RWD in West Asia or the Middle East and North Africa (MENA) region. The objective of this study was to describe the effectiveness and safety of tofacitinib in the treatment of ulcerative colitis in a Lebanese cohort.

Methods

This is a non-interventional, observational, retrospective cohort study. Data of patients meeting the inclusion criteria were extracted from an IBD database of the American University of Beirut Medical Center (AUBMC). Primary endpoints included the proportion of patients achieving clinical remission at 8, 26, and 52 weeks as per the assessment of the treating gastroenterologist, as well as the proportion of patients achieving endoscopic remission as determined by an endoscopic Mayo score of 0 or 1 at 24 weeks. Secondary endpoints included the persistence on tofacitinib treatment at 1 year, the proportion of patients requiring colectomy at 1 year, changes in calprotectin and C-reactive protein (CRP) at 12 weeks compared to baseline following treatment with tofacitinib.

De-identified data were collected from clinical practice of a number of experts in Lebanon and collated into a database at the American University of Beirut Medical Center. The study was approved by the Institutinal Research Board of the American University of Beirut The data collection occurred over a period of 4 months. The patients included were adult with confirmed diagnosis of UC who received treatment with tofacitinib with a minimum follow-up period of 12 weeks. Exclusion criteria included prior UC-related surgery, use of combination of tofacitinib with other biologic therapy, hospitalization with acute severe colitis, any previous use or exposure to tofacitinib. Data collected included demographics, disease phenotype, and prior biologic therapy, clinical and endoscopic assessments before and after tofacitinib treatment at weeks 8, 26, and 52 when available, treatment withdrawal and adverse events.

The bivariate analysis was conducted to determine if there was any association between the outcome and the exposure (the covariates). Unadjusted comparisons of baseline characteristics for 8, 26, and 52 weeks after complete remission against outcome measures are provided. Appropriate tests were used based on the measure's distribution: Fisher's exact test provided proportions, 1 sample t-test provided means, and 1-sample Wilcoxon test provided medians; p-values were also generated. Time to treatment failure is described using Kaplan-Meier estimates, and the median time to event is presented along with the 25th and 75th percentiles of treatment failure.

Results

In this retrospective cross-sectional national study, 60 patients with ulcerative colitis (UC) who were treated with tofacitinib between 2018 and 2021 were included.

The patient demographics and baseline characteristics are presented in Table 1. There were about the same number of female and male patients. The mean age was 34.5 years and the majority (58.3%) suffered for more than 5 years from ulcerative colitis. 58.3% of patients had received one or more biologics prior to tofacitinib. Only a minority of 8.3% did not take any other prior treatment.

About one-third of patients stopped tofacitinib treatment within the follow-up period, primarily for lack of efficacy or loss of response.

Clinical remission was reported in 25, 34, and 31 patients (41.7%, 56.7%, and 56.4%) at 8, 26, and 52 weeks, respectively. Please refer to Fig. 1. Please refer to supplementary Tables 2 and Table 3 for the details of the patients assessed at 8, 26, and 52 weeks respectively. Reduction in CRP levels were noted in 78.3% patients.

The findings of odds ratio calculation for achieving clinical remission based on patients' demographics and

Table 1 Patient demographics and disease characteristics ($n = 60$)

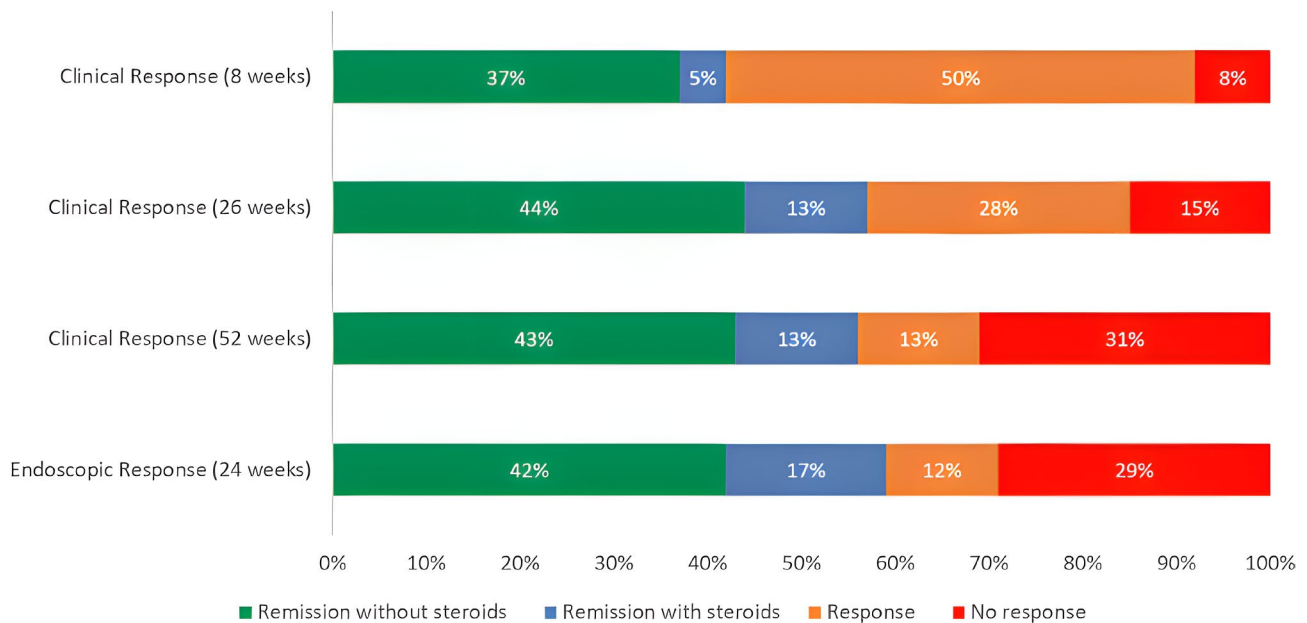| Variables	Categories	N (%)
Sex	Male	29 (48.3)
	Female	31 (51.7)
Mean age		34.5 ± 13.0
Smoking	Yes	14 (23.3)
	No	46 (76.7)
Duration of disease	2–5 years	24 (40.7)
	> 5 years	35 (58.3)
	Missing data	1 (1.7)
Mean years since diagnosis ($n = 59$)		7.9 ± 4.7
Prior biologics	None	25 (41.7)
	1 biologic	18 (30.0)
	More than one biologic	17 (28.3)
Other prior treatment	None	5 (8.3)
	5-ASA	25 (41.7)
	Immunomodulator	5 (8.3)
	5-ASA and immunomodulator	25 (41.7)
Extra-intestinal manifestations	None	49 (81.7)
	Peripheral arthropathy	5 (8.3)
	Axial involvement	1 (1.7)
	Pyoderma gangrenosum	1 (1.7)
	Uveitis	1 (1.7)
	More than 1 manifestation	3 (5.0)
Disease extent	Ulcerative proctitis	2 (3.3)
	Left-sided UC (distal to splenic flexure)	21 (35.0)
	Extensive (proximal to splenic flexure)	37 (61.7)
HZV testing	Yes	27 (45.0)
	No	29 (48.3)
	Data unavailable	4 (6.7)
HZV result ($n = 27$)	Positive	22 (81.5)
	Negative	5 (18.5)
Endoscopic Mayo score at initiation	3	37 (61.7)
	2	20 (33.3)
	Data unavailable	3 (5.0)
Method of Dispensation	Ministry of health	18 (30.0)
	NSSF (national social security fund)	24 (40.0)
	Self-payer	18 (30.0)
Induction dose period in weeks	4	4 (6.7)
	8	40 (66.7)
	12	4 (6.7)
	More than 12	6 (10.0)
	Stayed on same dose as induction	6 (10.0)

Fig. 1 Real world effectiveness of Tofacitinib in Lebanon: at 8, 26, 52 weeks and endoscopic response at 24 weeks

Table 2 Odds ratio for achieving clinical remission based on patients' demographics and disease specification

Variables	Categories	Adjusted OR (95% CI)		*P*-value
Age	≤ 30	1		
	> 30	5.252	(0.485, 56.828)	0.172
Sex	Male	1		
	Female	7.581	(0.785, 73.188)	0.08
Duration of disease (*n*=47)	2–5 years	1		
	> 5 years	5.373	(0.755, 38.242)	0.093
Disease extent	Proctitis or left-sided	1		
	Extensive	1.520	(0.209, 11.072)	0.679
Prior biologics use	No	1		
	Yes	0.092	(0.010, 0.864)	0.037
Reduction in CRP	No improvement	1		

disease specification are mentioned in Table 2. Only statistically significant factor determining increased chances of achieving clinical remission was prior use of biologics with odds ratio of 0.091 (95% CI – 0.010, 0.864), *p*=0.037.

Endoscopic remission (endoscopic Mayo score of 0 or 1) was observed in 58.3% of patients while the reduction of CRP was a significant variable to reach endoscopic remission in the odds ratio calculation (Supplementary Tables 5 and 6). The main difference in baseline characteristics to achieve clinical or endoscopic remission was found in the prior use of biologics and reduction in CRP (Table 3). Steroid-free clinical remission rates at 8, 26, and 52 weeks were 36.7%, 43.3%, and 43.6% respectively. The steroid-free endoscopic remission rate at 24 weeks was 41.7% The steroid-free combined endpoint of clinical and endoscopic remission was 32.1%.

Of all the patients (*n*=60) in the AUBMC database who were on tofacitinib between 2018 and 2021, 21 patients discontinued treatment; 19 of which were in the first year (Fig. 2).

The mean duration of therapy for patients remaining on treatment was around 2 years (24.3±9.5 months), and less than a year (10.4±6.1 months) for those who stopped treatment (*p*<0.001). The reduction of CRP was a significant factor (*p*=0.008) to determine if patients would be more likely to remain on tofacitinib or to discontinue treatment (Supplementary Table 7).

During the study, two adverse events were reported (1 lymphopenia and 1 facial acne) and were attributed to tofacitinib therapy based on treating physician assessment.

Discussion

In the present study, we assessed the real-world evidence on the effectiveness and safety of tofacitinib in ulcerative colitis in Lebanon. At the end of the study at 52 weeks,

Table 3 Difference in disease baseline characteristics and treatment specifications between patients achieving clinical and endoscopic remissions and those not achieving them. (*n* = 53)

Variable	Categories	No clinical and/or endoscopic remission	Clinical and endoscopic remission	Total	P-Value
Age	≤ 30	13 (44.8)	10 (41.7)	23 (43.4)	0.817
	> 30	16 (55.2)	14 (58.3)	30 (56.6)	
Sex	Male	16 (55.2)	11 (45.8)	27 (50.9)	0.498
	Female	13 (44.8)	13 (54.2)	26 (49.1)	
Smoking	No	22 (75.9)	18 (75.0)	40 (75.5)	0.942
	Yes	7 (24.1)	6 (25.0)	13 (24.5)	
Duration of disease (*n* = 52)	2–5 years	13 (46.4)	8 (33.3)	21 (40.4)	0.337
	> 5 years	15 (53.6)	16 (66.7)	31 (59.6)	
Disease extent	Proctitis or left-sided	9 (31.0)	9 (37.5)	18 (34.0)	0.621
	Extensive	20 (69.0)	15 (62.5)	35 (66.0)	
Extraintestinal manifestations	No	23 (79.3)	21 (87.5)	44 (83.0)	0.487*
	Yes	6 (20.7)	3 (12.5)	9 (17.0)	
Prior biologics use	No	9 (31.0)	15 (62.5)	24 (45.3)	0.022
	Yes	20 (69.0)	9 (37.5)	29 (54.7)	
Steroids use with tofacitinib	No	21 (72.4)	17 (70.8)	38 (71.7)	0.899
	Yes	8 (27.6)	7 (29.2)	15 (28.3)	
5-ASA use with tofacitinib	No	19 (65.5)	16 (66.7)	35 (66.0)	0.930
	Yes	10 (34.5)	8 (33.3)	18 (34.0)	
Reduction in CRP (*n* = 42)	No improvement	9 (42.9)	1 (4.8)	10 (23.8)	0.004
	Improvement or normal	12 (57.1)	20 (95.2)	32 (76.2)	

*Using Fisher's exact test
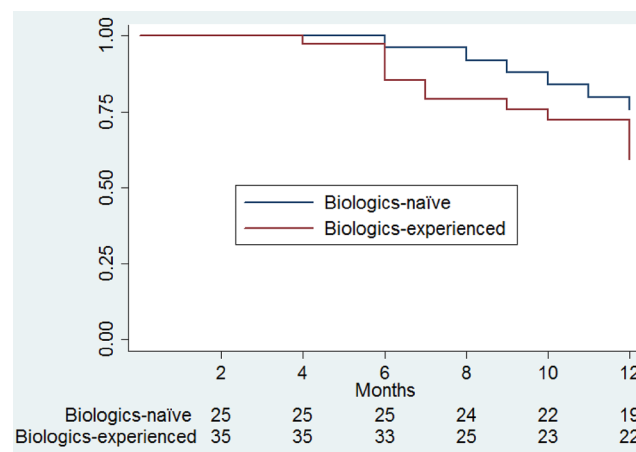
Fig. 2 Persistence on tofacitinib in the study cohort at one year stratified by biologics-exposure

56.4% patients achieved clinical remission and endoscopic remission was achieved in 58.3% patients at 24 weeks. Ever since tofacitinib has been approved for use, many real-world studies have attempted to evaluate its effectiveness and safety. However, our study is the first to discuss this in a MENA (Middle East and North Africa) region. This is a real-world evidence (RWE) study of UC patients with moderate to severe disease who received tofacitinib in Lebanon between 2018 and 2021 and followed up for at least 12 weeks. Most patients had either pancolitis or left-sided disease with endoscopic Mayo score of 2 or 3 at the time of initiation. Also, more than

half of them had failed one or more biologic therapy. This is also similar to most other previously reported RWE studies.

A meta-analysis of RWE studies of tofacitinib in UC patients was done by Lucaciu et al. [6], and included 830 patients from 9 different studies. Among the enrolled patients, 81% were previously treated with anti-tumor necrosis factor antibodies (TNF) and 57% were previously treated with vedolizumab. The clinical remission rate at 8 weeks was 37% compared to 41,7% in our study. Rate for remission at the median follow-up of 24 weeks was 29% compared to our rate at 26 weeks

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of 57%. Another recent meta-analysis and systematic review included 17 RWE studies with a total of 1162 UC patients: Remission (reported in 11 studies) was achieved in 34.7% of patients at week 8 (95% confidence interval [CI], 24.4-45.1%), 47% at weeks 12 to 16 (95% CI, 40.3-53.6%), and 38.3% at month 6 (95% CI, 29.2-47.5%). Corticosteroid-free remission (reported in 5 studies) was achieved in 38.4%, 44.3%, 33.6%, and 31% of patients at week 8, weeks 12 to 16, month 6, and month 12, respectively. Mucosal healing was achieved in 48.3% and 45.3% of patients at week 8 and weeks 12 to 16, respectively.

In our study, we also explored the potential explanatory variables associated with clinical and endoscopic remissions. One important factor was the prior use of biologics. Patients who are biologics experienced were less likely to achieve remission than biologics-naïve patients. On multivariate analysis, two variables were consistently associated with clinical and endoscopic remissions: biologic-naive status and a documented reduction in CRP. Patients who received prior biologics were 10 times less likely to achieve clinical remission at 1 year (OR=0.092, 95% CI=0.010, 0.864) than biologic-naïve patients. Patients who were biologic-naïve (11.6%) had a significantly higher rate of response at week 8 (1.38; 95% CI, 1.03–1.84). Patients with normalization or reduction in CRP values had higher odds (OR=78.47, 95% CI=2.094, 2940.317) than patients with no improvement in CRP at achieving clinical remission at 1 year. Similarly, patients with normalization or reduction in CRP were 19 times more likely to achieve endoscopic remission (OR=19.027, 95% CI=1.637, 221.087). When looking at both clinical and endoscopic remission, biologic-experienced patients were less likely to achieve this composite endpoint (OR=0.09, 95% CI=0.012, 0.655) than biologic-naïve patients. Patients with normalization or reduction in CRP had higher odds (OR=40.55, 95% CI=1.95, 845.15) than patients with no improvement in CRP in achieving this composite endpoint of clinical and endoscopic remission. However, more studies are needed to evaluate and validate this finding as this effect has not been observed/analyzed in prior real-world evidence studies.

In a study conducted by Straatmijer et al. between 2018 and 2019, 39% of patients had clinical and endoscopic remission at one-year follow-up, which is similar to our result of 45.3%. Also, the cessation of tofacitinib was seen in only one-third of the patients in both studies. In Straatmijer's study, it was reported that patients who failed prior anti-TNF were less likely to discontinue treatment. However, the sample size in this study was 36 patients with 89% of them with prior anti-TNF failure. This leaves only 4 patients without prior anti-TNF failure, which does not allow to draw any meaningful conclusions [7]. Another study that was done at multiple centers in the UK found that 74% of the patients responded initially to tofacitinib, compared to 92% in our study. However, the percentage of patients who had steroid-free remission at week 26 was 44%, which is the same result as our study at the same time point [4]. In a study conducted by Lair-Mehiri et al., the reported steroid-free clinical remission at 1 year was similar to our study (34% vs. 43%). In this study, surgery-free survival was also observed, and it was found that 70% of patients avoided colectomy at 1 year, while only 4 patients in our sample had colectomies, all of which their treatments were stopped [5].

With regards to the clinical and endoscopic evaluations from our study compared with the initial trial on tofacitinib conducted on 194 UC patients [8], comparable results were noted. Clinical remission at 8 weeks was achieved in 48% and 41% of patients on low and high doses of tofacitinib respectively, compared to 41.7% in our sample at the same time point. As for endoscopic evaluation, 61% of the low dose, and 78% of the high dose of the sample in the trial reached endoscopic remission after 8 weeks. In contrast, around 58% of our sample reached endoscopic remission at 26 weeks. This difference might be due to different observation times after treatment initiation, as patients can initially respond then fail the treatment.

In the study by Lucaciu et al., 32% of patients had at least one adverse event, the most commonly reported being mild infection (13%) and worsening of UC, requiring colectomy (13%) [6]. A third of the patients (35%) discontinued tofacitinib, most frequently due to primary non-response (51%). In the current study, similar proportion (35%; 21/60) of patients discontinued tofacitinib treatment.

One of the major limitations of this study is the small sample size and the retrospective nature of the study. The reason for lower enrollment rate can be attributed to the economic crisis in Lebanon, termination of financial coverage of the drug by the ministry of health and insurance companies, and the departure of many gastroenterologists and patients from the country, limiting assessment at different endpoint. Nonetheless, compared to other real-world evidence studies on tofacitinib, our study had higher or similar numbers. The retrospective nature of the study resulted in missing data for a few variables.

The current study showed similar results to other real-world evidence studies conducted on tofacitinib in UC patients in terms of clinical and endoscopic responses and remissions as well as the safety profile. Tofacitinib was effective in the treatment of moderately severe ulcerative colitis in this real-world cohort. Predictors of clinical and endoscopic remissions were biologic-naïve status and reduction in CRP. Observed AEs were consistent with the known safety profile. Larger studies and longer follow-up of real-world evidence are required to generate

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data on long-term effectiveness and safety of tofacitinib in UC.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03341-5.

> Supplementary Material 1

Data availability
The data that support the findings of this study are available from Pfizer and https://www.pfizer.com/science/clinical-trials/trial-data-and-results, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors Ala Sharara, Ayman Alrazim upon reasonable request and with permission of Pfizer. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Declarations

Ethics approval and consent to participate
Ethics approval for this study was granted by the Institutional Review Board (IRB) of the American University of Beirut (AUB). The need of consent was waived by IRB at AUB.

Consent for publication
Not applicable.

Competing interests
Dr Ala Sharara is an employee at AUBMC which had received funding for the conduct of this study. Marcelle Ghoubar is a full-time Pfizer employee. Other authors have no conflict of interest to declare.

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