

Point to point Reply

1) Why did the authors choose 1:3 case: control? Why not entire cohort?

From Jan. 2004 to Dec. 2015, a total of 905 patients were diagnosed with UC in our IBD clinic and median F/U period was 60 months (range 12 to 141 months; F/U period under 12 months were initially excluded for confirmative diagnosis of UC). Next, 286 UC patients whose follow-up period under 5 years were arbitrarily excluded because we planned to investigate the patients' clinical course and prognosis, so we needed enough follow period at least 5 years. Among 619 patients, initial rectal sparing UC patients were rare, 24 (3.9%). We thought the most significant limitation of our study is heterogeneity of cohort because this study is retrospectively designed. In particular, initial disease extent is very important in analysis of the prognosis as you know. For example, the prognosis of extensive colitis such as need for steroid or immunomodulator or surgery is more serious than that of less extensive UC. Therefore, we planned to match at least disease extent, age and sex to minimize the selection bias, and as a result, we concluded that three time the number ($\times 3$) was the maximal and appropriate number for our analysis to represent the control group. If we included entire cohort, the study group vs. control group was too inhomogeneous to draw a conclusion.

2) How many from the above 24+72 did they exclude based on follow-up inadequacy?

In our analysis, data follow-period less than 60 months were excluded already, so there was no additional exclusion because of follow-up inadequacy.

3) How many had change of diagnosis at followup?

As we mentioned in Result section, no diagnosis was changed from UC to CD. We think it is because we analyzed and initially included patient who were follow-up at least 12 months. (As mentioned above, a total of 905 patients were diagnosed with UC in our IBD clinic, F/U period ranges from 12 to 141m.)

4) Authors have not mentioned the inclusion or exclusion criteria with regard to topical corticosteroid/ mesalamine exposure in rectal sparing cohort. That will change the analysis

Initial diagnosis was very difficult (this is one of the important messages of our study) in a case of rectal sparing type UC. The rate of initial UC diagnosis was only 7/23 and therefore the evaluation of efficacy of topical mesalamine or steroid seems to be impossible. However, most of patients used only oral mesalamine, initially.

5) Were patients not started on azathioprine in steroid failure/dependency

In study group, all patients used azathioprine before biologics (1st ; anti-TNF) because of steroid failure (N=2) and dependency (N=2), but the optimal dose or duration was heterogeneous.

6) Please give the trajectory/ natural history of the patients from immunosuppression to each biological. Compare two groups and see if UC spared group had any peculiarities.

We added new table like this.

Table 3. Clinical history of UC patients who used biologics in both study and control group.

No.	Age at diagnosis	Sex	Initial endoscopic finding	Number of systemic steroid use	Indication for biologics	history of biologics	colectomy
1	21	F	RS	4	Steroid dependent	infliximab	-
2	30	F	RS	2	Steroid refractory	Infliximab (failed)	+
3	31	F	RS	9	Steroid dependent	golimumab	-
4	35	M	RS	2	Steroid refractory	Infliximab (failed)	+
5	15	F	RI	3	Steroid refractory	golimumab	
6	22	F	RI	1	Steroid refractory	Infliximab (failed)	+
7	20	F	RI	7	Steroid dependent	golimumab → tofacitinib	-
8	33	M	RI	4	Steroid refractory	infliximab	-
9	34	M	RI	2	Steroid refractory	Infliximab (failed)	+
10	35	M	RI	4	Steroid refractory	golimumab	-
11	39	M	RI	3	Steroid refractory	golimumab	-
12	41	F	RI	4	Steroid dependent	golimumab	-
13	44	M	RI	5	Steroid refractory	golimumab	-
14	48	M	RI	2	Steroid refractory	golimumab	-

RS; rectal sparing, RI; rectal involvement

7) If both groups have similar outcome, then what is the authors' hypotheses for this behaviour of rectal sparing UC? Discussion must clarify

We mentioned the hypothesis in discussion section as follows,

“As early detection of ulcerative colitis is possible thanks to the easy availability of colonoscopy and advanced imaging techniques, we can hypothesise that atypical pattern of colonoscopic findings in a patient with ulcerative colitis can be observed more frequently. In fact, in our data, most of the UC patients with rectal sparing showed rectal lesion during the follow-up examination, which means that the atypical distribution of mucosal inflammation may be found temporarily at an early stage”