

# Does co-treatment with immunosuppressors improve outcome in patients with Crohn's disease treated with adalimumab?

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## SUMMARY

### Background

There is clear benefit from combination therapy with infliximab and immunosuppressive drugs (IS), but few data are available for adalimumab (ADA).

### Aim

Our aim was to assess the efficacy of ADA monotherapy and ADA+IS for induction and maintenance therapy in Crohn's disease.

### Methods

Retrospective study of patients with Crohn's disease treated with ADA in Oxford, UK or Liège, Belgium. Treatment periods were divided into 6-month semesters. A combination therapy semester was defined as ADA+IS for at least 3 months; successful induction meant clinical response; a semester with flare as ADA dose escalation, starting steroids, perianal complication, or surgery; and ADA failure as ADA withdrawal for secondary loss of response or intolerance. Semesters with and without flares were compared through univariate and multivariate analysis.

### Results

Successful induction was achieved in 171/207 (83%) patients, with no significant difference between ADA+IS and ADA monotherapy (85% vs. 82%,  $P = 0.50$ ). Five hundred and sixty-two semesters in 181 patients were included for maintenance analysis. ADA+IS was not associated with fewer semesters with flare (34% vs. 35%,  $P = 0.96$ ), or with ADA failure (6% vs. 8%,  $P = 0.43$ ). Nevertheless, combination therapy in the first semester was associated with a lower risk of ADA failure (5% vs. 10%,  $P = 0.04$ , OR = 0.48) and combination therapy beyond 6 months was associated with fewer semesters with flares (14% vs. 36%,  $P = 0.02$ , OR = 0.31).

### Conclusions

There may be a benefit from ADA+IS combination therapy during the first semester of initiating ADA, with a slight decrease in ADA failure and lower need for ADA dosage escalation.

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## INTRODUCTION

The benefit of concomittant oral immunosuppressive drugs with scheduled anti-TNF maintenance therapy has been established for infliximab (IFX),<sup>1</sup> but remains unclear for adalimumab (ADA), although combination therapy is routinely used with all anti-TNF agents in rheumatological practice.<sup>2</sup> Concomittant immunosuppressive (IS) drugs, including azathioprine (AZA), mercaptopurine (MP), or methotrexate (MTX), appear to reduce the risk of antibody formation to the drugs, which are associated with lower trough levels, shorter time to relapse and infusion reactions.<sup>3, 4</sup> In IS-naïve patients with relatively early Crohn's disease treated with IFX, the prospective Study Of biologic and immunomodulator Naive patients In Crohn's disease (SONIC) trial clearly demonstrated the benefit of combination therapy with IFX and AZA.<sup>1</sup> In patients with longer duration of Crohn's disease, many of whom had already been exposed to IS in clinical practice, a retrospective study from Paris also suggested a potential benefit of IFX+IS combination therapy, at what ever stage IS was combined with IFX.<sup>5</sup> Few data are available for ADA. In the pivotal registration study of ADA (Crohn's trial of the fully Human Antibody adalimumab for Remission Maintenance, CHARM), post-hoc analysis did not detect any impact of IS co-treatment on the remission rate achieved at 1 year.<sup>6</sup> The Leuven group also reported no more treatment failure in patients on ADA monotherapy than combination therapy, but a slightly shorter time to drug escalation.<sup>7</sup> The aim of our study was to assess the impact of ADA+IS combination therapy on the rate of response to ADA induction, as well as its effect on flares of Crohn's disease or treatment failure during maintenance therapy with ADA in routine clinical practice.

## METHODS

### Patients

All patients ever treated with ADA for Crohn's disease at the John Radcliffe Hospital, Oxford, UK and CHU Sart Tilman, Liège, Belgium, were considered for inclusion. The diagnosis of Crohn's disease was based on standard criteria,<sup>8</sup> with disease distribution and behavior as most recently assessed at the time of ADA therapy.<sup>9</sup>

### Study design

Retrospective analysis of 6-month treatment periods (semesters) for induction success and efficacy of maintenance therapy during a minimum 12-month period, for

flare or treatment failure, comparing semesters with and without combination therapy.

### Induction success

For the assessment of response to induction, only patients with at least 3 months' exposure to ADA were considered (Figure 1). Combination therapy for induction was defined as a patient who had received 3 months of ADA+IS during the induction period, with IS started at least 3 months before commencing ADA. Induction success was evaluated at 3 months, defined as a clinical response or remission as determined by the gastroenterologist at a routine clinical visit.

### Maintenance efficacy

For the assessment of maintenance efficacy, only patients with at least 12 months' continuous treatment with ADA were analysed (Figure 1). The treatment period was divided into semesters (below). Combination therapy (ADA+IS) for maintenance was defined as a minimum 3 months' IS treatment during a semester, with AZA (2–2.5 mg/kg), MP (1–1.5 mg/kg), or MTX (15–25 mg/week administered orally or by injection). Thiopurine therapy was optimised by weight or leucocyte count, but not by metabolite monitoring.

### Semesters

A semester was defined as a 6-month period with ADA. A *flare semester* was defined as deterioration in clinical symptoms requiring treatment modification (ADA reinduction, escalation to weekly ADA injection, initiation of corticosteroids, or switch to another biologic), new perianal complication, or abdominal surgery for active CD. A *remission semester* was a semester without a flare on ADA every other week, or de-escalation from ADA

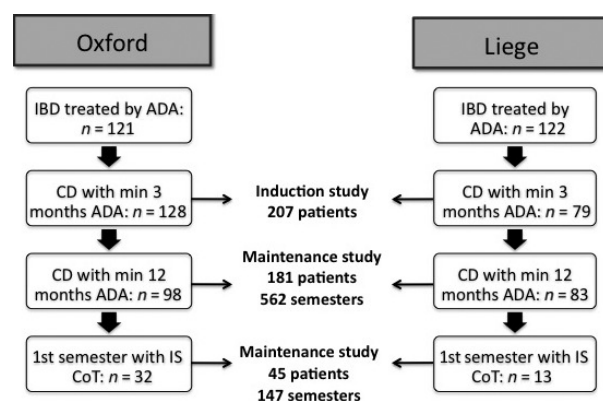


Figure 1 | Patient recruitment.

1 weekly to every other week and without a flare during  
 2 the 2 following months. A *failure semester* was defined  
 3 as ADA withdrawal for secondary loss of response, or  
 4 intolerance. The *semester total* was the cumulative num-  
 5 ber of semesters on treatment. ADA *interruption* was  
 6 defined as interrupted therapy for >4 weeks for any rea-  
 7 son (flare, surgery, infection, pregnancy, or cessation  
 8 during remission). *Re-starting* ADA was considered to  
 9 be a new treatment period, so more than one treatment  
 10 period with ADA was possible for each patient.

### 11 Analysis of semesters

12 Analysis of flare semesters and failure semesters com-  
 13 pared semesters on ADA monotherapy and ADA+IS  
 14 combination therapy. Each semester was analysed sepa-  
 15 rately. Overall analysis excluded the first semester and  
 16 incomplete semesters, with a separate analysis of the sub-  
 17 group of patients exposed to IS during the first semester  
 18 of ADA therapy, similar to that performed in a previous  
 19 study for IFX.<sup>5</sup> In the group of patients treated with ADA  
 20 +IS during the first semester, subpopulations of *IS failure*  
 21 (who had failed IS treatment in the months before start-  
 22 ing ADA) and of *IS others* (meaning those who were  
 23 naive to IS, or who started IS at the same time as ADA,  
 24 or who for some reason had ADA started without evi-  
 25 dence of active disease, such as post-operatively) could be  
 26 identified, so were evaluated separately, as well as a com-  
 27 parison between thiopurines (AZA or MP) and MTX.  
 28

### 29 Statistical analysis

30 Descriptive statistics are expressed as mean (standard  
 31 deviation) for continuous variables and as numbers (per-  
 32 centages) for qualitative variables. Induction success was  
 33 assessed by comparing proportions achieving clinical  
 34 response or remission on ADA monotherapy and ADA  
 35 +IS during induction using Chi-square test. Multivariate  
 36 logistic regression analysis was performed after univariate  
 37 analysis had identified factors potentially associated with  
 38 successful induction.  
 39

40 Maintenance efficacy was assessed by comparing pro-  
 41 portions of semesters with flare and failure, for semesters  
 42 on ADA monotherapy and ADA+IS in the whole popu-  
 43 lation using Chi-squared test.

44 The risk of flare according to the semester total and  
 45 type of IS was studied using generalised estimated equa-  
 46 tions.<sup>10</sup> Demographic and clinical factors potentially asso-  
 47 ciated with a flare semester or failure semester were first  
 48 analysed using univariate analysis: the factors were age,  
 49 gender, weight, age at diagnosis, disease duration, age at  
 50 diagnosis according to Montréal classification, current

CD location, current CD behaviour, current perineal dis-  
 ease, previous surgery, number of previous operations,  
 smoking habit, family history of IBD, spondylarthropathy,  
 previous use of IFX, ADA, or certolizumab pegol, ADA  
 induction regimen, CRP at ADA start, ADA+IS and ADA  
 +IS during the first semester, and centre (Oxford/Liège).  
 Variables with a *P*-value <0.10 in univariate analysis were  
 considered for multivariate logistic regression analysis.  
 A *P*-value <0.05 was considered significant.

The group of patients treated with IS during the first  
 semester of ADA therapy was then analysed using the  
 same approach. Proportions of subsequent flare semes-  
 ters on ADA monotherapy and ADA+IS semesters and  
 factors associated with flare and failure semesters were  
 studied using univariate and multivariate analysis, using  
 the same factors as the whole population apart from  
 ADA+IS during the first semester.

The proportion of semesters with flare on ADA+IS  
 was compared between patients with IS failure and those  
 with IS tolerant at ADA start using a Chi-squared test.  
 ADA+thiopurine semesters and ADA+MTX semesters  
 were also performed using Chi-squared test. Calculations  
 were performed using the 9.2 version SAS logiciel (SAS  
 Institute, Cary, NC, USA).

## RESULTS

### Patient characteristics

A total of 243 patients with IBD (239 Crohn's disease, 2  
 ulcerative colitis, 2 IBD unclassified) exposed to ADA  
 were screened for inclusion. Those without a definite  
 diagnosis of Crohn's disease, or who did not meet the  
 criteria of 3 months' treatment with ADA for assessing  
 induction success or 12 months' for maintenance efficacy  
 were excluded. We identified 207 patients suitable for  
 the evaluating induction success (Oxford *n* = 128, Liege  
*n* = 79) and 181 patients (Oxford *n* = 98, Liege *n* = 83)  
 suitable for evaluating maintenance efficacy (Figure 1).  
 Among these, 45 had received ADA+IS during the first  
 semester and were further analysed separately. Our retro-  
 spective analysis identified only one severe adverse event:  
 an episode of severe pneumonia requiring intensive care  
 for 4 days in a patient on ADA monotherapy during the  
 third semester of ADA treatment. Patient characteristics  
 are described in Table 1.

### Impact of ADA+IS on the response to ADA induction (*n* = 207)

The rate of successful ADA induction was 171/207 (83%)  
 at 3 months. ADA was started with IS in 74 patients

**Table 1** | XXXXXXXXXXXXXXXXXXXXXXXXXX

Patients characteristics	Induction study N = 207 (%)	Maintenance study: Patients treated 12 months with ADA N = 181 (%)	Maintenance study: Patients treated with ADA+IS during the 1st semester N = 45 (%)
Age (years, mean ± s.d.)	33 ± 11	33 ± 11	33 ± 13
Male gender	79 (38)	75 (41)	19 (42)
Weight (kg)	67 ± 16	67 ± 14	68 ± 16
Age at diagnosis (years, mean ± s.d.)	22 ± 9	27 ± 8	21 ± 9
Disease duration (years, mean ± s.d.)	11 ± 8	12 ± 10	11 ± 8
Age at diagnosis			
A1	44 (21)	44 (24)	14 (31)
A2	154 (74)	131 (73)	29 (65)
A3	9 (5)	6 (3)	2 (4)
Current disease location			
L1	24 (12)	23 (12)	2 (4)
L2	51 (24)	41 (23)	12 (27)
L3	132 (64)	100 (55)	24 (53)
L4*	23 (11)	19 (10)	7 (15)
Current disease behavior			
B1	122 (59)	94 (52)	27 (60)
B2	56 (27)	55 (30)	11 (24)
B3	28 (14)	32 (18)	7 (16)
Active perianal disease	113 (55)	91 (50)	26 (58)
Surgery	68 (34)	90 (50)	15 (33)
Number of surgeries			
0	102 (49)	91 (50)	30 (67)
1	64 (31)	51 (28)	6 (13)
2	16 (8)	16 (9)	3 (7)
≥ 3	25 (12)	23 (13)	6 (13)
Smoking habit	68 (34)	66 (38)	15 (36)
Family history of IBD			
No	142 (83)	123 (81)	28 (78)
1st degree	13 (8)	11 (7)	2 (5)
≥ 2nd degree	15 (9)	18 (12)	6 (17)
Spondylarthropathy	3 (1)	5 (3)	0 (0)
Previous Infliximab	132 (64)	114 (63)	33 (73)
Previous Adalimumab	25 (12)	18 (10)	3 (7)
Previous Certolizumab	14 (7)	14 (8)	3 (7)
ADA induction regimen			
160/80	142 (69)	124 (70)	31 (72)
80/40	20 (10)	20 (11)	6 (14)
none	33 (16)	25 (14)	4 (9)
Unknown	12 (5)	12 (5)	4 (5)
CRP at ADA start (mg/L, mean ± s.d.)	22 ± 31	19 ± 27	15 ± 25
ADA+IS during 1st semester	NA*	63 (35)	45 (100)
ADA+IS semesters	NA	90 (16)	56 (38)
ADA treatment duration (months, mean ± s.d.)	44 ± 51	26 ± 11	27 ± 11
Severe adverse events	0 (0)	1 (0.5)	1 (2)
Semesters	NA	562	147
Centre Oxford/Liège	79/128 (38/62)	98/83 (54/46)	32/13 (71/29)

No patients had isolated L4; all patients with L4 had concomitant L1, L2 or L3 involvement.

\* NA, Non applicable.

(36%) and the response to ADA induction did not differ between the group started on ADA monotherapy and the group started on ADA+IS (82% and 85% respectively,

$p = 0.50$ ). This group included those ( $n = 47$ ) already on IS for  $\geq 3$  months at commencement of ADA, subject to separate analysis. In the multivariate analysis, two inde-

pendent factors were associated with failure of ADA induction: high CRP (44 mg/L vs. 18 mg/L,  $P = 0.01$ , OR = 1.02, 95% CI: 1.01–1.03) and age under 16 at diagnosis ( $P = 0.02$ , OR = 4.08, 95% CI: 1.49–11.15).

**Impact of ADA+IS on maintenance in the whole population ( $n = 181$ )**

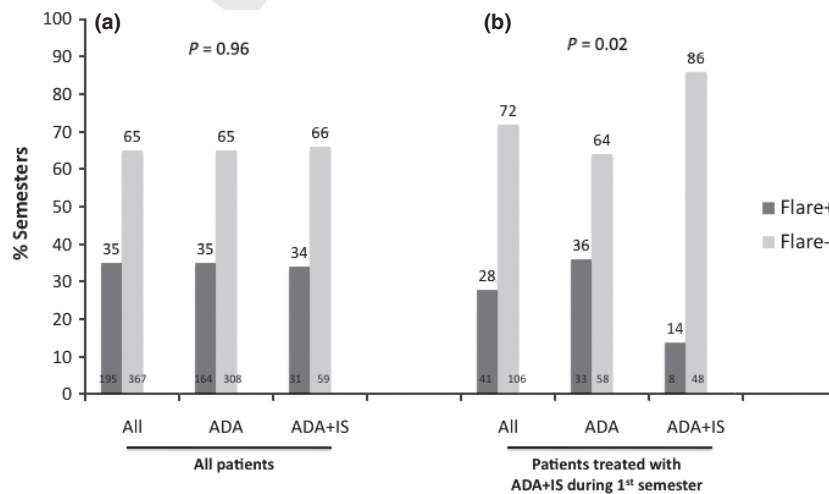
Five hundred and sixty-two semesters were analyzed, including 472 semesters on ADA monotherapy and 90 semesters on ADA+IS (thiopurine  $n = 65$ , MTX  $n = 25$ ). The mean semester total for follow-up was 4 (range: 2–9).

The rate of semesters with flare in the whole population was 35% ( $n = 195$ ) and no difference was observed between semesters with ADA monotherapy and semesters with ADA+IS (35% and 34% respectively,  $P = 0.96$ ) (Figure 2a). The large majority of semesters with flare corresponded to the need for escalation to ADA weekly dosing ( $n = 157$ , 81%). We identified 18 semesters with surgery (9%), 19 with new perianal complications (10%), 1 with a switch to IFX (0.01%), 12 with ADA reinduction (7%) and 20 with corticosteroid prescriptions (10%). No significant differences were observed regarding the need for surgery ( $P = 0.05$ ) or new perianal complications ( $P = 0.21$ ) between ADA monotherapy or ADA+IS (Table 2). There were no more failures in ADA+IS semesters compared with ADA monotherapy semesters (6% and 8% respectively,  $P = 0.43$ ) in the whole population (Figure 3a). The rate of flare semesters was stable

over time ( $P = 0.90$ ) and did not change according to ADA±IS ( $P = 0.08$ ). In multivariate analysis, semesters with flares were associated with four independent factors: active perianal disease ( $P = 0.02$ , OR = 1.57, 95% CI: 1.07–2.32), previous surgery ( $P < 0.01$ , OR = 1.89, 95% CI: 1.31–2.87), female gender ( $P = 0.01$ , OR = 1.68, 95% CI: 1.12–2.52) and Liège centre ( $P < 0.01$ , OR = 1.94, 95% CI: 1.31–2.87). Independent factors associated with the risk of new perianal complications and abdominal surgery are shown in Table 3. ADA+IS was not an independent parameter associated with flare semester. Concerning ADA failure, the only independent factor after multivariate analysis was ADA+IS during the first semester ( $P = 0.04$ , OR = 0.48, 95% CI: 0.24–0.97). No

**Table 2 | All CD patients ( $n = 181$ ): Semesters with IBD activity according to ADA±IS. The rate of semesters with flare was not significantly different between patients treated with ADA monotherapy and patients treated with ADA+IS. Regarding the type of flare, surgery, new perianal complication or ADA dose escalation, no difference was demonstrated between the 2 groups**

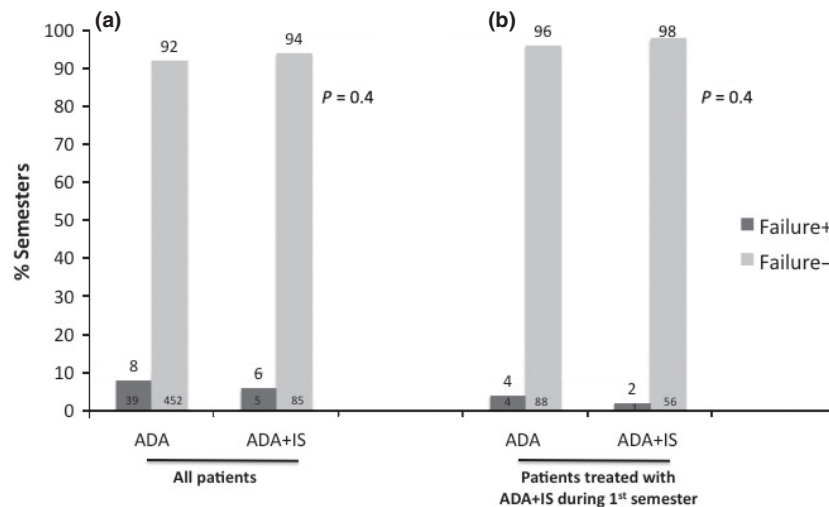
N (%)	ADA monotherapy	ADA+IS	P-value
IBD flare	164 (35)	31 (34)	0.96
Surgery	12 (7)	6 (19)	0.06
Perianal complications	18 (11)	1 (3)	0.2
ADA dose escalation	104 (81)	53 (80)	0.95



**Figure 2 | Semesters with flare according to ADA±IS. (a).** In the whole population (562 semesters in 181 patients), the rate of semesters with flare was not statistically different between semesters with ADA monotherapy and ADA+IS ( $P = 0.96$ ). **(b)** In the patients treated with ADA+IS during the first semester (147 semesters in 45 patients), flares were statistically less frequent in semesters with ADA+IS (14%) compared to ADA monotherapy (36%) ( $P = 0.02$ ).

LOW RESOLUTION FIG





**Figure 3** | Semesters with ADA failure according to ADA±IS. In the whole population (a) (562 semesters in 181 patients) and in the patients treated with ADA+IS during the first semester (b) (147 semesters in 45 patients), the rate of semesters with ADA failure was not statistically different between semesters with ADA monotherapy and ADA+IS ( $P = 0.4$ ).

**Table 3** | Independent risk factors for surgery and perianal complication in the whole population ( $n = 181$ )

	P-value	OR (95% Confidence limits)
Surgery ( $n = 18$ )		
Male gender	<0.01	13.16 (3.29–52.63)
Disease duration	0.01	1.12 (1.01–1.21)
Active perianal disease	0.02	5.51 (1.30–23.15)
Oxford centre	<0.01	8.8 (2.29–34.24)
Perianal flare ( $n = 19$ )		
Active perianal disease	0.01	7.74 (1.65–36.22)
Oxford centre	0.03	3.33 (1.14–9.77)

other independent factor, including semester with ADA+IS, was identified. The risk of semester with failure was 10% vs. 5% in patients with ADA monotherapy in the first semester and ADA+IS respectively.

#### Impact of ADA+IS on maintenance in patients treated during the first semester with ADA+IS ( $n = 45$ )

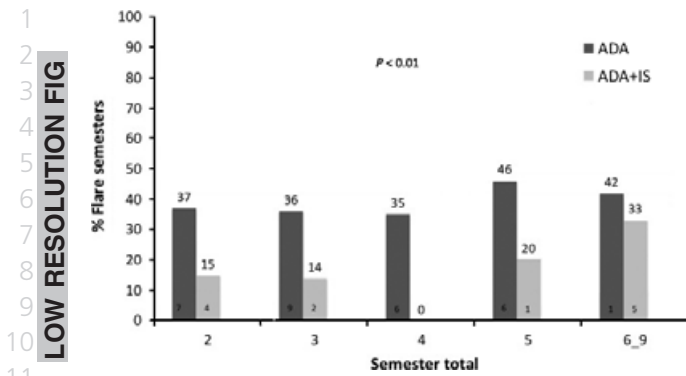
Forty-five patients received ADA+IS during the first semester and were analysed separately (147 semesters, including 91 subsequent semesters with ADA monotherapy and 56 with ADA+IS). Analysis of this subgroup of patients demonstrated that flares were less frequent in semesters with continued ADA+IS compared with semesters with ADA monotherapy (14% and 36% respectively,  $P = 0.02$ , OR = 0.31, 95% CI: 0.12–0.81)

(Figure 2b). The rate of flare did not change over time ( $P = 0.86$ ) and the protective effect of ADA+IS was stable according to the semester total ( $P < 0.01$ ) (Figure 4). Flare semester characteristics were as followed: ADA weekly ( $n = 35/41$ , 86%), abdominal surgery ( $n = 3$ , 7%), perianal complications ( $n = 3$ , 7%), corticosteroids ( $n = 22\%$ ). There were no more semesters with ADA failures in semesters with ADA+IS compared with semesters with ADA monotherapy (2% and 4% respectively,  $P = 0.41$ ) (Figure 3b). Among those patients on IS at initiation of ADA, the proportion of semesters with flare did not differ between patient having failed IS or not before ADA start ( $P = 0.86$ ). Furthermore, there was no significant difference between semesters with ADA+thiopurine and ADA+MTX ( $P = 0.84$ ).

In multivariate analysis, three independent factors were significantly associated with flare semesters: ADA monotherapy ( $P = 0.02$ , OR = 3.28, 95% CI: 1.25–8.3), previous surgery ( $P = 0.01$ , OR = 3.69, 95% CI: 1.57–8.68) and Liège centre ( $P = 0.01$ , OR = 3.17, 95% CI: 1.40–7.19). Factors specifically associated with the risk of new perianal complications and abdominal surgery were not analysed because of the small number of events in this subgroup. No clinical or demographic factors were associated with ADA failure.

## DISCUSSION

Although the benefit of IS in patients treated with IFX has been clearly demonstrated both in IS naïve and IS



**Figure 4 | Semesters with flare according to ADA±IS and semesters total in the patients treated with ADA +IS during the first semester (147 semesters in 45 patients). The rate of semesters with flare was stable over the time ( $P = 0.86$ ). The protective effect of ADA +IS compared to ADA monotherapy for a flare semester did not change according to the semester total ( $P < 0.01$ ).**

exposed patients, the benefit of such combination therapy is not well documented with ADA. In this retrospective analysis, we could not show any benefit of ADA+IS for achieving induction success for clinical response and remission. In maintenance ADA therapy, we could also not show any decrease in semesters with flares during semesters with ADA+IS combination therapy. This is consistent with the results of the subanalysis of the CHARM trial,<sup>6</sup> but at odds with the practice-based French study on IFX.<sup>5</sup>

Nevertheless, there was a benefit of combination therapy (ADA+IS) when IS had been given during the first semester of ADA treatment. This was associated with half the rate of ADA failure over the subsequent semesters. Although this was quantitatively small (from 10% to 5%), it is likely to be clinically as well as statistically significant. Furthermore, among these patients treated during the first semester with ADA+IS, there were fewer semesters with flares during subsequent maintenance treatment with ADA+IS compared with semesters on ADA monotherapy, suggesting a sustained benefit.

The large majority of semester flares were characterised by escalation in ADA dosage. On subanalysis, it was only prevention of dose escalation with ADA that benefited from continued ADA+IS combination therapy after having been treated by this combination in the first semester, not other definitions of flares, including new perianal complications or abdominal surgery, although numbers (19 and 18/195 semesters with abdominal oper-

ations and new perianal complications respectively) in the latter groups were very small. A similar benefit of ADA+IS was suspected by the Leuven group who noted a shorter time to ADA dose escalation, but no excess of treatment failure on ADA monotherapy.<sup>7</sup>

Combination therapy with IS can reduce anti-TNF antibody formation and improve the pharmacokinetics of anti-TNF drugs.<sup>11, 12</sup> It has also been demonstrated that discontinuation of ADA due to treatment failure is associated with low ADA trough level concentrations.<sup>7</sup> In our study, the benefit of combination therapy at the time of starting ADA, whether or not continued after the first semester, might be explained by early inhibition of anti-ADA antibody formation, leading to higher trough levels from the start of the therapy that could predict long-term efficacy of ADA. An alternative explanation might simply be better control of the inflammation on combination therapy from the onset of treatment that reduces the risk of relapse compared with ADA monotherapy. Prospective studies combined with anti-ADA antibody and ADA trough level measurements are required to validate these hypotheses.

Apart from combination therapy in the first semester, among the factors associated with flare semesters, were previous surgery and being treated in Liège. Although previous abdominal surgery is consistent with more severe disease,<sup>11</sup> the association with Liège deserves a specific comment. In the current study, fewer in the Belgian cohort received IS than the British cohort, but weekly treatment with ADA was more common in Belgium. As the commonest reason for defining a flare was dose escalation on monotherapy, this treatment strategy is reflected in the increased rate of flares in Liège compared to Oxford. In contrast, surgery and perianal complications were more frequent in Oxford, but accounted for only a small proportion of flares. These results may reflect easier access to anti-TNF therapy in Belgium. Indeed, the Belgian healthcare system allows easier access to long-term anti-TNF therapy as well as dose escalation, whereas the British healthcare system encourages shorter treatment duration with a higher threshold for dose escalation. This might explain why, in similar clinical circumstances, patients may be treated in Belgium with weekly ADA monotherapy, but in the UK with ADA every other week in combination with IS or even surgery.

Our study was closely modelled on that of Sokol *et al.*,<sup>5</sup> who demonstrated a benefit of IS+IFX compared with IFX monotherapy using semester-based analysis. However, in their study, only patients receiving IFX+IS

during the first semester were included, which corresponds to our subgroup of 45 patients (157 semesters) treated with ADA+IS during the first semester. In their study, IFX+IS was associated with fewer semesters with dose escalation or interval reduction compared with subsequent semesters on IFX monotherapy. In this respect, we confirm a similar result in those on ADA+IS during the first semester, with fewer needing ADA dose escalation in subsequent ADA+IS semesters compared with ADA monotherapy. The Sokol study<sup>5</sup> also reported fewer perianal complications or switches in biological therapy in IFX+IS semesters, but no impact on the frequency of semesters with abdominal surgery. These events were too rare to analyse in our population. Furthermore, 70% of our patients had already been treated by another anti-TNF agent (usually IFX) before ADA; hence, switch biological therapy in the Sokol study might be compared with ADA failure in our study. Although Sokol *et al.*<sup>5</sup> found a modest decrease in the need to switch to another biologic during IFX+IS semesters, we found no benefit of prolonged ADA+IS beyond the first semester. This is more comparable to the results in the Leuven cohort and IMID trial.<sup>12</sup>

Our study has several limitations due mainly to its retrospective nature. First, the definition of the flare was retrospective and included different clinical situations (e.g. starting steroids, dose escalation, surgery, etc.). Second, patients were not randomised between ADA monotherapy and ADA+IS, hence these two populations are not strictly comparable. Third, there were no serum samples to measure trough levels or anti-ADA antibodies. Fourth, data on the intake and the dose of corticosteroid during the induction time with ADA were missing for half of the patients, although just 5% of all data in the induction group were missing. Although the available data did not show any influence of corticosteroids on the response to ADA induction, an effect cannot be excluded; hence, a

lack of influence of steroids on response to ADA cannot be concluded. Nevertheless, in this retrospective analysis from the experience of two referral centers, the benefit of ADA+IS appears limited to those co-treated at the start of ADA therapy. Combination therapy with ADA during the first semester slightly decreased the rate of ADA failure during maintenance therapy independently of whether ADA+IS was continued beyond the first semester. During maintenance therapy, ADA+IS was associated with a lower rate of ADA dose escalation.

We think our results may help clinicians decide whether to use ADA in monotherapy or combination therapy, particularly, with regard to the potential benefits from such combination at the start of ADA. Accordingly, it seems reasonable to start with the combination and then continue ADA monotherapy after about 6 months of combination therapy, as the need for dose escalation does not appear to be affected after the first semester. The choice of the treatment strategy needs to be balanced with potential risks of infection and cancer and also with the cost of the strategy. In older patients with high comorbidity, or younger male subjects at increased risk of hepatosplenic T-cell lymphoma<sup>14</sup> on combination therapy, stopping the IS 6 months after ADA start seems a reasonable option. It is also not unreasonable to give ADA as monotherapy from the start as long as the slight increase in the absolute risk of treatment failure is recognised. A randomised trial is needed to confirm whether ADA+IS is more effective than ADA monotherapy, particularly to examine whether any benefit is limited to combination therapy in the first semester, and whether it simply decreases the need for ADA dose escalation, or whether it also decreases clinically relevant measures of patient outcome.

## ACKNOWLEDGEMENT

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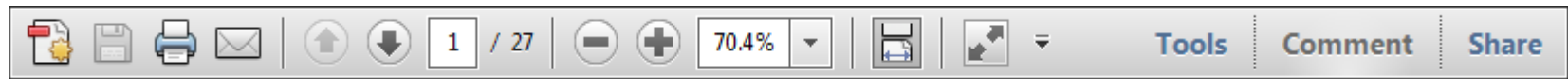
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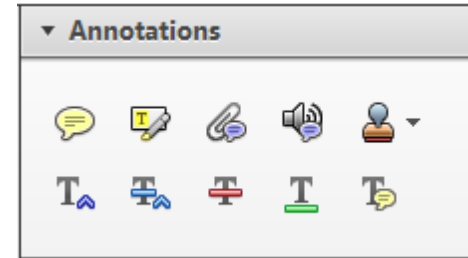
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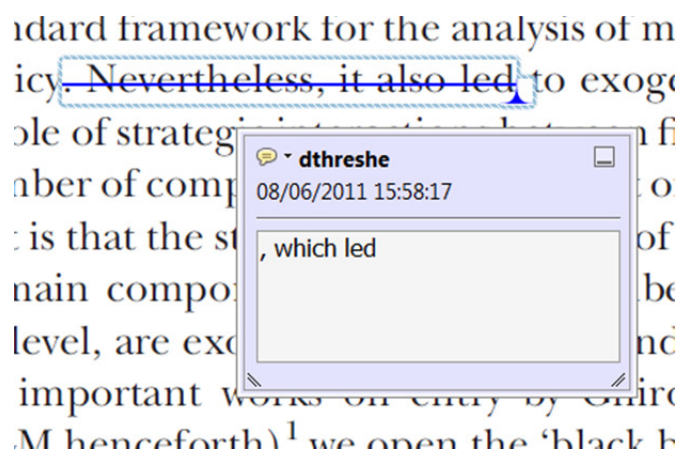
**1. Replace (Ins) Tool – for replacing text.**



Strikes a line through text and opens up a text box where replacement text can be entered.

**How to use it**

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- Click on the [Replace \(Ins\)](#) icon in the Annotations section.
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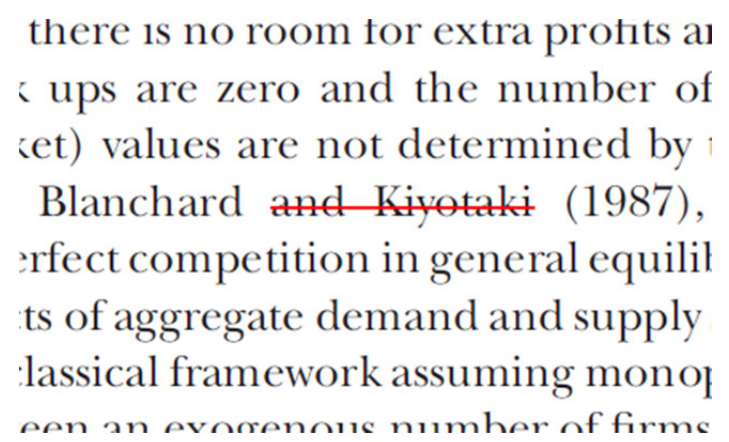
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Strikes a red line through text that is to be deleted.

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- Highlight a word or sentence.
- Click on the [Strikethrough \(Del\)](#) icon in the Annotations section.



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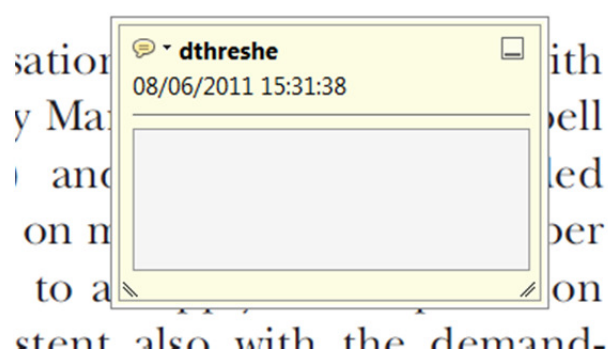


Highlights text in yellow and opens up a text box where comments can be entered.

**How to use it**

- Highlight the relevant section of text.
- Click on the [Add note to text](#) icon in the Annotations section.
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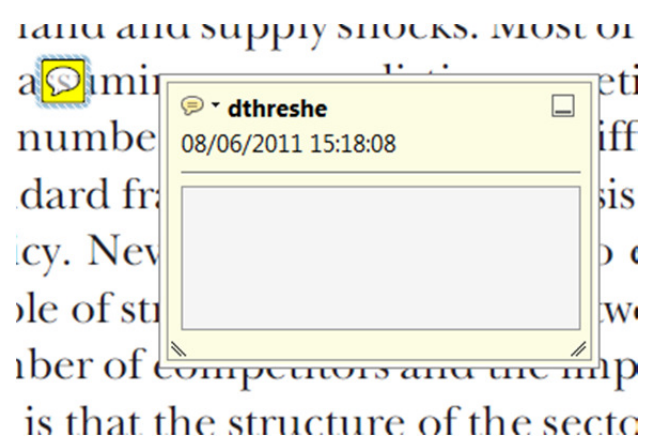
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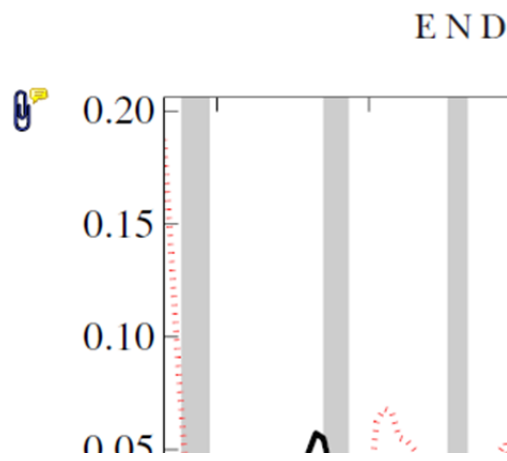
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Inserts an icon linking to the attached file in the appropriate place in the text.

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- Click on the [Attach File](#) icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
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Inserts a selected stamp onto an appropriate place in the proof.

**How to use it**

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- Select the stamp you want to use. (The [Approved](#) stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).

of the business cycle, starting with the  
 on perfect competition, constant return  
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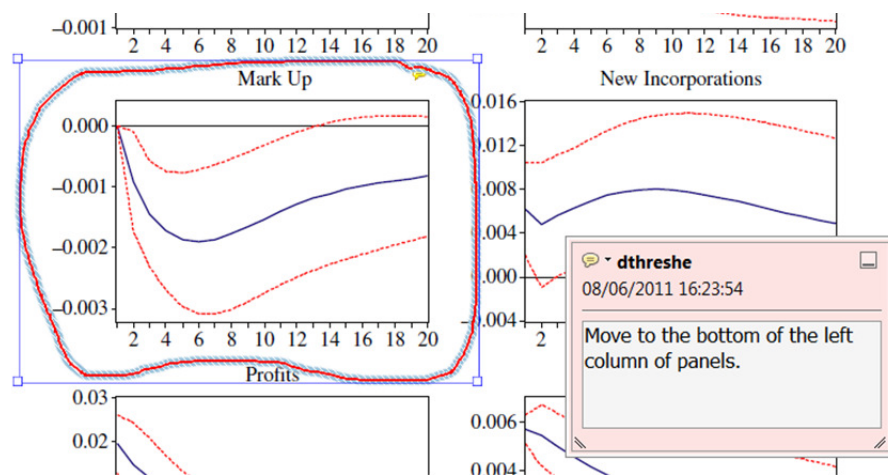


**7. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.**

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