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ORIGINAL ARTICLE

Regression of fibrosis after HBV antiviral therapy. Is cirrhosis reversible ?

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antiviral therapy – chronic hepatitis B – hepatocellular carcinoma – liver fibrosis

Abbreviations
ADV, adefovir; CHB, chronic hepatits B; ETV, entecavir; HCC, hepatocellular carcinoma; LAM, lamivudine; NAS, nucleos(t)ide analogs; TBV, telbivudine; TFV, tenofovir.

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Abstract

Long-lasting HBV-DNA suppression is considered to be the best surrogate end-point of antiviral therapy in patients with hepatitis B virus (HBV) related chronic hepatitis or cirrhosis, and it is a prerequisite to prevent liver-related complications and improve survival. Treatment with oral antiviral drugs in patients with HBV cirrhosis is effective in restoring liver function and improving survival even in those with decompensated cirrhosis. These agents are generally well-tolerated for long-term treatment, and several evidences have demonstrated that they are able to reverse liver fibrosis and prevent the occurrence of HCC.

In patients with HBV related cirrhosis, antiviral therapy with nucleoside or nucleotide analogues (NAs) should be initiated as soon as the diagnosis has been established. European Association for the Study of the Liver (EASL) Clinical Practice Guidelines (1) suggest that antiviral treatment of HBV cirrhosis is indicated to prevent viral reactivation whatever the serum HBV-DNA levels.

In fact, there is a significant correlation between HBV DNA levels and necroinflammatory activity (2) and since liver fibrosis is mainly stimulated by hepatic necroinflammatory activity (3), the fibrogenetic process could be reduced as a result of the suppression of HBV.

The main goals of antiviral therapy are to prevent liver decompensation, the occurrence of hepatocellular carcinoma (HCC) and to improve survival. However, numerous studies have been performed to assess the progressive changes in liver histology with long-term antiviral therapy. Indeed, even if this is only a surrogate outcome it could help improve the prognosis of HBV related liver damage.

Although advanced liver fibrosis was previously thought to be irreversible, there is evidence to show that cirrhosis can be reversed if the underlying cause of liver injury is eliminated (4–14). The purpose of this review is to collect the available data from literature focusing the issue of reversibility of liver fibrosis after antiviral therapy in Chronic Hepatitis B.

Natural course of chronic HBV infection

The natural history of chronic HBV infection and disease is complex, thus understanding the clinical outcomes and the factors affecting disease progression is important in the management of this entity (15). Fattovich *et al.* (16) performed a systematic review in 2008 assessing the rate of disease progression and the factors influencing the course of liver disease.

The 5-year cumulative incidence of cirrhosis was 8 and 17% in East Asian countries and European countries, respectively, in patients with HBeAg positive chronic hepatitis and 13 and 38%, respectively, in patients with HBeAg negative chronic hepatitis. When they present with compensated cirrhosis at least 30–70% of patients still have active viral replication, which is associated with continued liver disease progression and decreased survival over time (17, 18).

Among host factors, older age is an important determinant of progression to cirrhosis and HCC since it is related to a longer duration of HBV liver disease. Male gender has been also identified as an independent risk factor of cirrhosis (19, 20) and the overall risk of HCC

in chronic HBV carriers is three to six times higher in men than in women (21, 22). The antifibrogenic effect of oestrogen probably explains this association (23).

The incidence of hepatic decompensation and/or oesophageal varices bleeding was 3–4 per 100 person years in patients with early stages of cirrhosis in both European and Asian studies, with a 5-year cumulative incidence of liver decompensation of 15% (5, 24–26).

Decompensation usually presents with at least one episode of ascites, jaundice, hepatic encephalopathy or variceal bleeding (27). This can develop insidiously or as a complication of an acute hepatitis flare (28). The latter was demonstrated in a study showing that hepatic decompensation developed in 14% of patients with cirrhosis who experienced hepatitis flares (29). The prognosis of these two modes of hepatic decompensation have not been clearly differentiated and compared. Other hepatitis virus superinfections in HBV patients with cirrhosis other than active HBV replication could cause decompensation (16, 30).

Once hepatic decompensation occurs, mortality increases significantly, ranging from 70 to 85% at 5-year follow-up in different studies (25, 31). These patients need to be carefully evaluated. Evaluation of patients with cirrhosis includes liver function status, and the presence of varices. Monitoring of HCC in patients with HBV cirrhosis is mandatory.

The efficacy of antiviral therapy in patients with HBV cirrhosis

Therapy must provide sufficient virological suppression to achieve biochemical remission, histological improvement and the prevention of complications. The ideal outcome is HBsAg loss which unfortunately is infrequent. Moreover, complete eradication of hepatitis B virus (HBV) infection in chronic hepatitis B is not achieved with current therapies. Even in patients who clear HBsAg, HBV remains in infected hepatocytes in the form of covalently closed circular DNA (cccDNA) for the lifetime of the cell, thus, a more realistic goal of therapy is sustained or maintained virological remission (32).

Drugs available for the treatment of CHB include interferon (IFN), PEG-IFN and five NAs. NAs for HBV therapy can be classified into nucleosides (lamivudine, LAM; telbivudine, TBV; entecavir, ETV) and nucleotides (adefovir, ADV; tenofovir, TFV).

Interferon based therapy

Interferon based therapy is not frequently used in patients with cirrhosis. Indeed, even if it has certain advantages such as finite duration, the absence of resistance and higher rates of anti-HBe and anti-HBs seroconversion, there is only a moderate antiviral effect, poor tolerability and a high risk of adverse events (1).

Thus, there is not enough evidence to determine the histological improvement of patients with HBV related cirrhosis following IFN. However, numerous studies have shown how conventional IFN therapy or more recently PEG-IFN can reduce the progression of fibrosis and the occurrence of liver decompensation and HCC both in HBeAg positive and HBeAg negative patients (33–37). A significant reduction in the incidence of cirrhosis (17.8% vs 33.7% in the controls; $P = 0.041$) has been demonstrated (33) in a large cohort of HBeAg-positive patients treated with IFN compared with well-matched untreated patients.

Furthermore, an earlier randomized control study showed that IFN therapy reduced the incidence of HCC in patients with HBeAg-positive active chronic hepatitis (34).

Moreover, HBeAg-negative patients who achieved a sustained viral response (SVR) following IFN showed a decrease in the progression of the Ishak fibrosis score or a decreased risk of cirrhosis as well as fewer severe cirrhosis-related complications in the long term, a reduced incidence of HCC, less need for liver transplantation and lower mortality. Unfortunately, a SVR occurred in less than 30% of HBeAg-negative patients (35, 36).

Interferon-based therapy has been shown to be safe in patients with compensated cirrhosis (37) also suggesting that patients with cirrhosis can benefit from IFN based treatment.

A recently published meta-analysis showed a significant reduction in the risk of HCC ranging from a 34% reduction in patients with chronic hepatitis to 47% in patients with cirrhosis (38). Two other meta-analyses have confirmed that IFN therapy significantly prevented the development of HCC. (10, 39).

Nucleoside and nucleotide analogues

Five different antiviral agents have been approved and treatment with these oral agents has been shown to be life-saving. LAM and ADV and more recently ETV), 3
TBV and TFV have revolutionized the treatment of chronic hepatitis B (40). These treatments can delay the progression of fibrosis and reverse both fibrosis and cirrhosis (3, 4, 7, 8), Table 1. Furthermore, they prevent hepatic decompensation in patients with advanced fibrosis and cirrhosis (5, 41, 42).

Lamivudine

LAM was the first oral agent licensed for the treatment of hepatitis B. Clinical trials have shown that LAM therapy can delay the progression of fibrosis, reduce progression to and reverse cirrhosis, prevent liver decompensation in patients with cirrhosis and stabilize patients with hepatic decompensation (4, 5, 43).

In a study from Asia (5), continuous LAM therapy delayed clinical progression in CHB patients and advanced fibrosis or cirrhosis by reducing the incidence of hepatic decompensation and HCC. Similarly, an Italian multicentre study designed to evaluate the clinical

Table 1. Rate of the regression of fibrosis in patients with chronic hepatitis B and cirrhosis treated with nucleos(t)ide analogues.

	Patient N.	HBsAg status	Regression of fibrosis				Reference
			1	2	3	5 (yr)	
Lamivudine	30	+			67%		4
Adefovir	16	−				75%	6
	15	+				60%	9
	90/125	±				49%/12%	49
Entecavir	10	±				100%	11
	57	±				96%	12
	(10*)		40%			100%	
Tenofovir	133	±	27%			68%	14
	(96*)	±				74%	49
	176/250					71%/67%	
Telbivudine	921/446	±		65%/67%			51

*Patients with cirrhosis

outcome of chronic HBV in relation to virological response to LAM (41) found that HBeAg-negative patients with cirrhosis and with a SVR were less likely than those with viral breakthrough to develop HCC and disease progression, and that survival was better in patients with Child A cirrhosis and SVR.

The direct effect of LAM monotherapy on portal pressure in CHB cirrhosis was evaluated in a prospective study by Manolakopoulos *et al.* (42). The results of this study show that virological and biochemical response to LAM is associated with a significant decrease in portal pressure in patients with cirrhosis and clinically significant portal hypertension (hepatic venous pressure gradient >10 mmHg).

Although LAM has the most extensive safety record, the high rate of viral breakthrough because of virological resistance to LAM (up to 30% in year 1 and up to 70% at the end of 5 years) and the availability of more potent and effective agents with improved resistance profiles, has reduced its use in patients with chronic hepatitis B especially those with cirrhosis in whom loss of virological response can lead to clinical deterioration.

Adefovir dipivoxil

Although ADV is less potent than LAM, it has mainly been used for LAM-resistant chronic hepatitis B and hepatic decompensation associated with LAM-resistance prior to and after liver transplantation (1, 44). Indeed, the advantage of this drug was its limited resistance for 1–2 years and the absence of cross-resistance with LAM and other L-nucleosides. Long-term (>3 years) ADV therapy resulted in the improvement of fibrosis or the reversal of advanced fibrosis (6, 9). Marcellin *et al.* (9) have shown a significant histological improvement (defined as a reduction of at least 2 points in the Knodell necroinflammatory score with no worsening of the Knodell fibrosis score) in 60% of patients treated with ADV and with liver biopsy before and after antiviral therapy. Hadziyannis *et al.* (6) observed a significant improvement in liver histology following long-term treatment with ADV.

In this large trial, liver biopsies after 192 (placebo-ADV group) or 240 weeks (ADV group) of treatment showed that necroinflammation improved in 86% and 83% of patients, respectively, and fibrosis improved in 73 and 75%, respectively, compared with pretreatment biopsies.

In a long-term follow-up study of the 226 waiting list patients and 241 post-transplant patients with recurrent hepatitis B because of LAM-resistant HBV, the use of ADV resulted in undetectable HBV DNA in 65% of the waiting list and post-transplant patients after 96 weeks of therapy. Moreover, after 48 weeks of treatment, liver function improved in 50–80% of these patients (44).

Like LAM this drug has been gradually replaced by more recent NAs because of the resistant variants that increase after the first year and reach almost 30% after 4 years (1).

Entecavir

Entecavir (ETV) is a potent inhibitor of viral replication in chronic hepatitis B. In a recent study, an Italian group evaluated the efficacy of ETV in an Italian cohort of unselected patients with different stages of liver fibrosis, comparing the virological and clinical results between patients with and without cirrhosis (45). This study 4 showed that results with ETV were excellent for patients with HBV liver disease and especially cirrhosis where there was a good tolerability profile, better efficacy and an earlier virological response.

Schiff *et al.* (11) evaluated the improvement in liver histology in 10 patients with advanced fibrosis or

cirrhosis (Ishak fibrosis score 4–6), who received long-term ETV treatment (approximately 6 years, range, 267–297 weeks). All patients had liver biopsies at baseline, week 48, and long term, and histological improvement of at least 1-point on the Ishak fibrosis score was found in all patients after long-term treatment. Similarly, in a study by Chang *et al.* (12), 96% of patients (55/57) had histological improvement after long-term treatment with ETV. Ten of the 57 patients had advanced fibrosis or cirrhosis (Ishak score 4–6) at the baseline. All 10 patients achieved at least a 1-point reduction in the Ishak fibrosis score after long-term ETV therapy.

Also there was a 6.37-point reduction in the mean Knodell necroinflammatory score after long-term treatment vs a mean reduction of 3.39 points after 48 weeks of ETV therapy.

A more recent study analysing 372 ETV-treated patients including 98 patients with cirrhosis, showed that the virological response to ETV is associated with a lower probability of disease progression (liver decompensation and HCC) in patients with cirrhosis (13).

Finally, Shim *et al.* (46) prospectively compared the efficacy of ETV in 70 patients with decompensated cirrhosis and 144 patients with compensated CHB. There was no significant difference between the groups in the percentage of patients who achieved undetectable HBV DNA or ALT normalization and HBeAg seroconversion or HBeAg loss after 6 or 12 months of treatment. The Child–Pugh score (CPS) and the Model for End Liver Disease (MELD) score was significantly improved in decompensated patients treated for >12 months and the 2-year cumulative rates of HCC and death or liver transplantation were 6.9 and 17% respectively.

Tenofovir

TFV, the most recently approved drug for hepatitis B, is more potent, more rapid and has a better resistance profile than ADV as well as an excellent safety profile. There are very few data on the outcome of patients with cirrhosis and TFV.

In the study by Marcellin *et al.* (47), histological improvement was obtained in significantly more patients who received TFV than in those who received ADV (71% vs. 49% in HBeAg-negative patients and 67% vs. 12% in HBeAg- positive patients). Necroinflammation was reduced in most patients. More recently, another study evaluated the histological improvement (≥2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis) and regression of fibrosis (≥1 unit decrease by Ishak scoring system) in a large cohort of patients treated with TFV (14). At baseline 38% (133/348) of the patients had bridging fibrosis to cirrhosis (Ishak scores of 4 or more), but this rate declined to 28% (97/344) and 12% (42/348) at year 1 and year 5 respectively. Overall, the regression of fibrosis occurred in 51% (176/348) of patients and histological improvement in 304/348 (87%) of patients after 5 years of treatment. Figure 1.

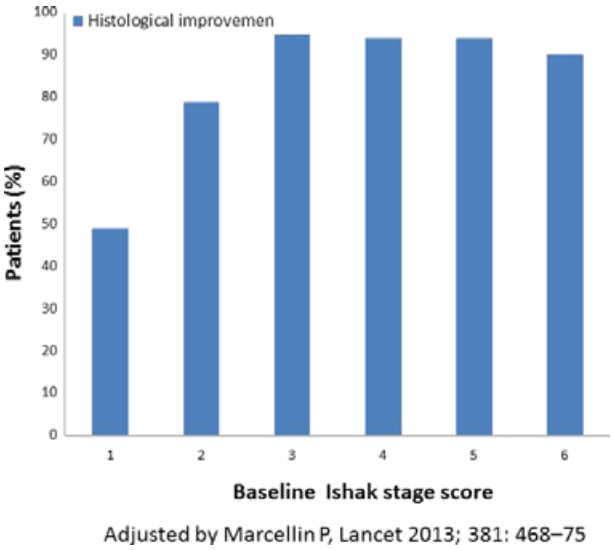

Figure 1. Histological response at year 5 according to baseline Ishak fibrosis scores for 348 patients with data available at baseline and year 5 (Marcellin P, Lancet 2013;381: 468–75). 10

Finally a 2 point reduction in the CPS occurred in 48% of patients with liver decompensation treated with TFV compared with 41.7% treated with ETV, and a median reduction in the MELD score of 2.0 from baseline was reported for both groups (48).

Telbivudine

There are only few data evaluating the real effects of TBV on histological improvement in patients with chronic hepatitis B. In HBeAg-positive patients, TBV seems to be better than LAM in achieving histological improvement (65% vs 56%) but not in obtaining biochemical (77% vs 75%) or serological responses (HBeAg seroconversion in 23% vs 22%). On the contrary, in HBeAg-negative patients, TBV suppressed HBV DNA to undetectable levels in 88% of patients vs 71% of patients treated with LAM but histological improvement (67% vs 66%) and biochemical improvement (74% vs 79%) was not different between the two groups (49).

Conclusion

The goal of treatment for chronic HBV infection is to achieve viral suppression, control liver fibrosis and prevent progression to hepatic decompensation and HCC. Hepatic fibrosis is mainly stimulated by hepatic necroinflammatory activity, and several studies have shown that prolonged antiviral therapy is associated with improvement in liver histology and even reversal of cirrhosis in chronic HBV infection.

However, the evidences available so far, involved a small proportion of patients enrolled in the trials, and consisted of a small number of patients with advanced fibrosis or cirrhosis. Moreover, there is the bias because of selection of patients to undergo repeat biopsy and furthermore the important issue of the correct stain for elastic fibres in liver biopsies. Indeed, mostly in presence of high grade of necroinflammation, there is a parenchymal collapse simulating septa, and in these cases collagen stains (Sirius Red, Masson Thricrome) could lead to a misdiagnosis of cirrhosis which could be evaluated as disappeared in the successive liver biopsies.

In our opinion the amount of liver fibrosis, if correctly evaluated, could be reduced by a switching off of inflammation but we need more and well-designed studies to assess whether the distorted liver parenchyma and altered blood flow in the cirrhotic liver are reversible.

This review has provided an update on these data. All NAs have been shown to improve liver histology in patients with CHC and this is especially true in patients with advanced fibrosis. Improvement in both necroinflammation and the stage of fibrosis prevents decompensation and HCC, significantly changing the prognosis of patients with HBV cirrhosis. For this reason both patients with compensated and decompensated cirrhosis should be promptly and correctly treated with oral antiviral therapy whatever the HBV DNA level as early as possible (Fig. 1).

Available antiviral drugs are safe and effective in improving liver function in this population although only the use of ETV and TFV is highly recommended because of their low risk of resistance.

Acknowledgement

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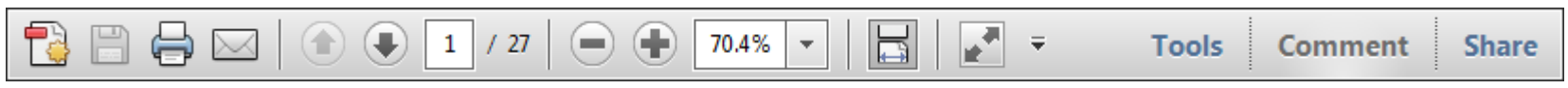
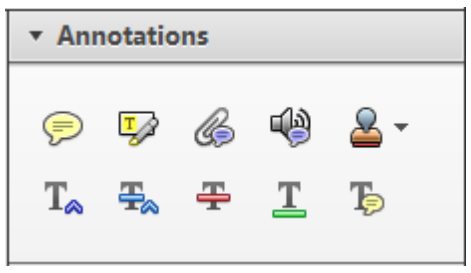


This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

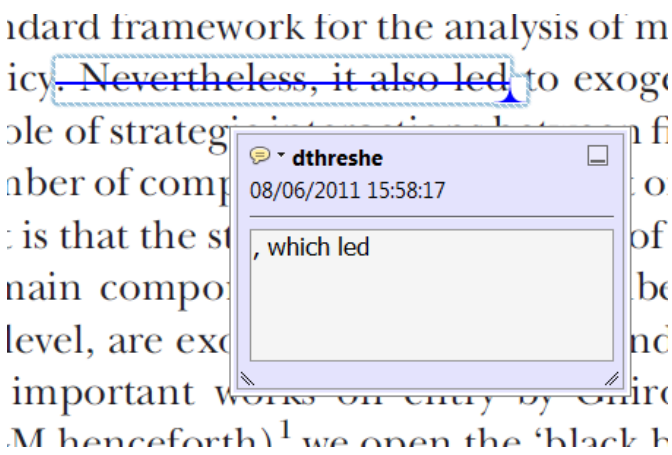


1. Replace (Ins) Tool – for replacing text.

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

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

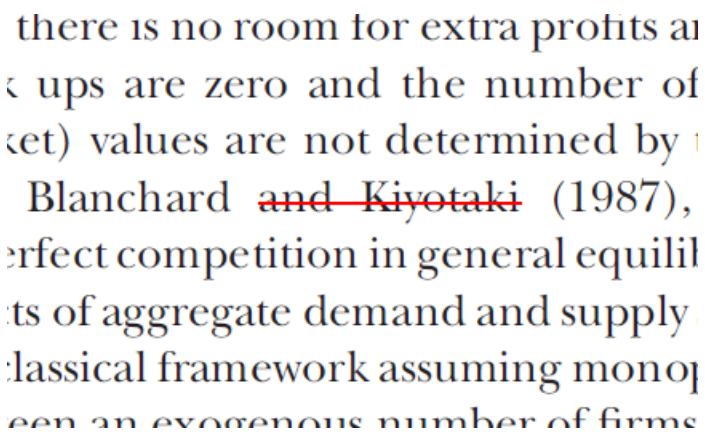


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

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

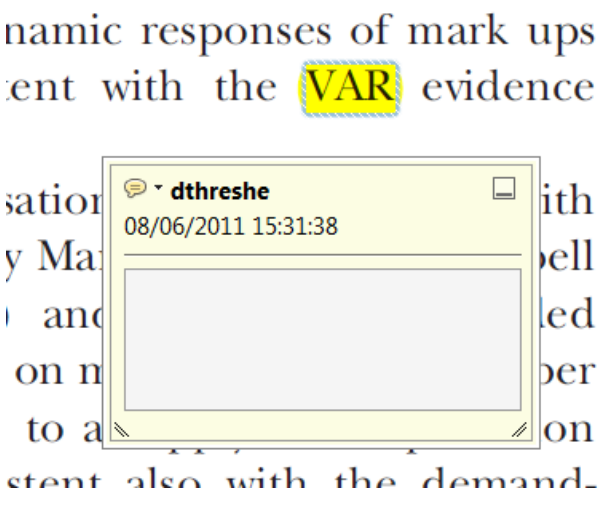


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

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.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

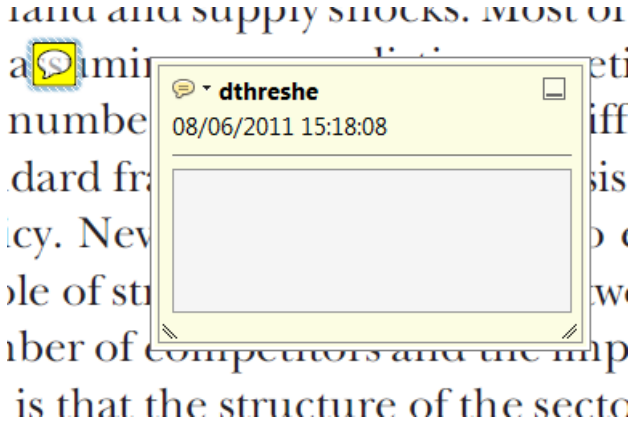


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.



WILEY-BLACKWELL

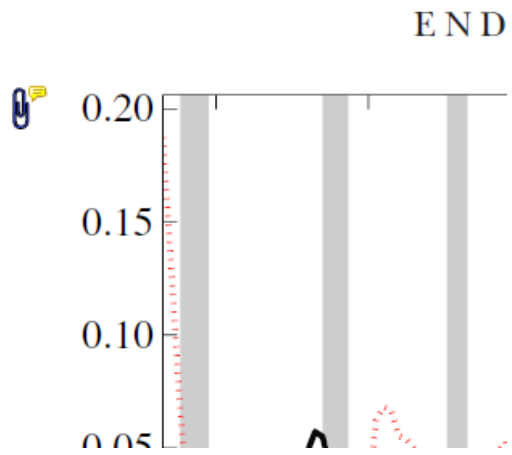
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate pace in the text.

How to use it

- 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.
- Select the colour and type of icon that will appear in the proof. Click OK.

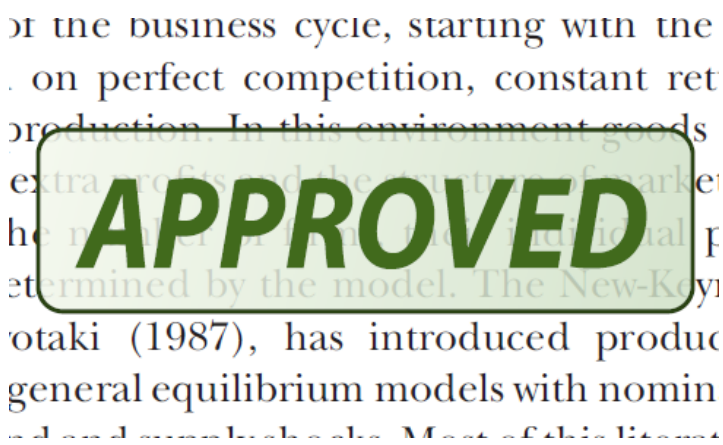


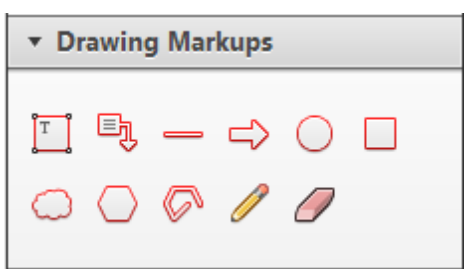
6. Add stamp Tool – for approving a proof if no corrections are required.

Inserts a selected stamp onto an appropriate place in the proof.

How to use it

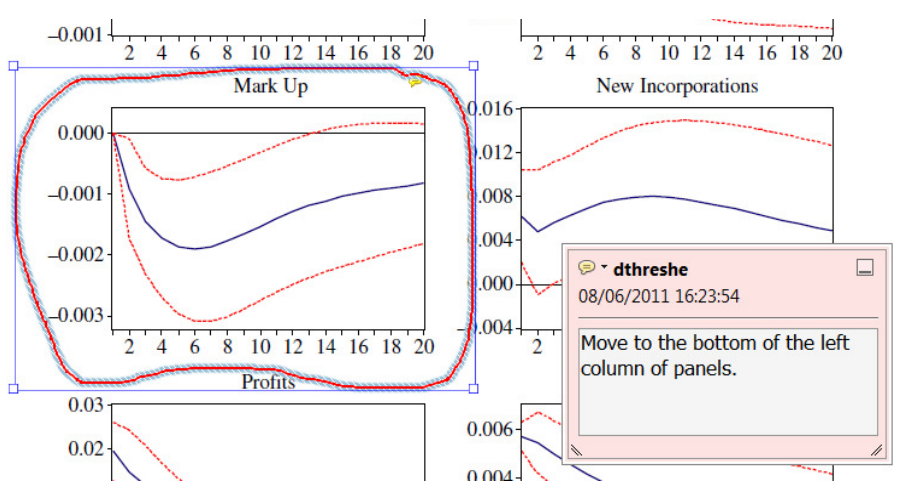
- Click on the Add stamp icon in the Annotations section.
- Select the stamp you want to use. (The Approved stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the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





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

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..



How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.

For further information on how to annotate proofs, click on the Help menu to reveal a list of further options: