# CAT (T) is Out of the Bag

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The much anticipated results of Comparison of AMD Treatment Trial (CATT) were out a few weeks ago. CATT study is a landmark trial in comparative clinical research. Indeed, the study was not sponsored by the pharmaceutical industry instead it was supported by National Eye Institute (NEI), USA. Dr Martin and his colleagues are to be applauded for undertaking such a high quality study. For this study to take place various laws governing use of medications and reimbursement in the USA had to be amended. The study was published in New England Journal of Medicine[1] and an editorial by Dr. Philip Rosenfeld (the father of Avastin) was published in the same issue[2].

## BACKGROUND

NEI launched the CATT Study in 2008 to compare Avastin and Lucentis for treatment of neovascular AMD. The aim of the study was to compare monthly Lucentis, monthly Avastin, as needed (PRN) Lucentis and PRN Avastin treatment regimens. Patients were randomly assigned and treated with one of the four regimens. CATT is a non-inferiority study. Under the rules of the trial, patients treated with Avastin could read on average of up to five fewer letters on an ETDRS chart than those treated with Lucentis and Avastin would still be considered "non-inferior". To allow for six pair-wise comparisons with a 99% confidence interval, a sample size of 300 patients in each group was required (n=1200).

In PRN groups, after a single injection, further injections were given on an as needed basis. Patients were followed up every month with clinical examination and OCT. Note that unlike PrONTO study[3], the patients in the PRN arms, were not given 3 loading injections at the start. Injections were repeated whenever deemed appropriate based on the clinical and OCT findings. It is worth noting that the study had much broader "real world" inclusion criteria of "active AMD", compared to previous AMD studies where the inclusion criteria had been quite narrow.

## RESULTS

The study has now reported one-year results for 1,185 patients treated at the 43 clinical centers in USA. When considering 5 letters difference as a clinically meaningful effect, there was no statistical difference between the groups. Note that in previous trials for AMD a meaningful effect was defined as 3 or more lines on EDTRS (15 letters). Therefore, the study was powered to pick even a small difference between the efficacy of Lucentis and Avastin.

The groups were also similar in other visual acuity measures as well: those who gained 3 lines, avoided 3 lines loss, or achieved at least 20/40 vision.

The mean decrease in central retinal thickness was

greater in the Lucentis-monthly group (196 µm) than in the other groups (152 to 168 µm, P=0.03 by analysis of variance). Does this translate into reduced vision at the final follow up (month 24) is yet to be seen.

In the first year of the study, time domain OCT was used. In the second year of this study spectral domain OCT will be used. Higher resolution SD-OCT may result in increased detection of fluid and subsequent treatment. Because patients in the fixed monthly dosing arm received injections every month regardless of the OCT, using a higher resolution SD-OCT is likely to have a selective effect on the PRN arms of the study.

**SAFETY ISSUES**

In contrast with the one-year results, which suggested that Lucentis might be somewhat safer than off-label Avastin, major adverse events during the trial's second year appeared to be about equal. In the NEJM manuscript one year adverse events were reported. However, at the ARVO annual meeting principal authors of the study reported that rates of death, stroke, and all arterio-thrombotic events were equal between the two drugs during the trial's second year ($p>0.20$) (Table 2). This is reassuring, as these side effects have been highlighted as areas of concern in previous studies.

The frequency of serious adverse events (SAEs) (= hospitalisation for any cause) was marginally higher in Avastin compared to Lucentis group (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66). There was no statistical difference when the 4 groups were compared separately, however when Avastin monthly and as needed groups, and Lucentis monthly and as needed arms, were stacked up there was a marginal difference ($p=0.04$). However, in a study of multiple comparisons, one would expect a *p* value of <0.01 to be statistically significant.

The study was not powered to pick up rare but serious adverse events. It is estimates that a study to prove safety differences between the drugs, if any, would require a much larger sample size of up to 20,000 patients. The differences in this study are probably a chance finding because:

1. There were imbalances in baseline health between Avastin and Lucentis patients. More of the former had diabetes, hypertension, congestive heart failure and other medical conditions. Additionally, patients in Avastin group were one year older.
2. Excess events were broadly distributed across many disease categories (eg. pneumonia, surgical procedures, fractures, etc). These were not identified in previous cancer trials as areas of concern – when Avastin was used at 500 times higher dosage.
3. There were more SAEs for both drugs when they were used less (eg. in PRN groups).

Does this mean that we are putting our patients at increased risk of a hip fracture or urinary tract infection by treating less often? Most would agree that it is unlikely the events are even remotely related.

Let us not forget previous drug safety controversies, including rosiglitazone and the COX-2 inhibitors. Small increases in risk seen in controlled clinical trials and in epidemiological studies were not followed up appropriately. Therefore, continued pharmaco-vigilance and further robust studies are needed to prove any real safety differences between the two drugs.

**COST**

Lucentis - $2,000 (About Rs 80,000 in Pakistan) per injection.

Avastin- $50 (Rs 1000-3,500 in Pakistan) per injection

In addition to providing effective and safe treatment to our patients, we must remain mindful of the health economic implications of high-cost therapies. Roche sells Lucentis in the United States and Novartis in other countries. Sales of the drug for each company were about $1.5 billion last year.

**ANTI-VEGF NON-RESPONDERS**

We know that there are patients who simply do not respond to anti-VEGF treatment. It is possible that some unknown genetic factors determine this response. The CATT study will hopefully help answer this question as well. All patients in the trial underwent genetic testing. The results will be matched against drug response and outcomes. The genetic information gathered will be extremely important in understanding different treatment response. Perhaps patient specific genetic profiling will allow us to customize most appropriate treatment for individual patient.

**Table 1:** Mean gain in visual acuity and number of injections at 1 year.

| | Lucentis | Avastin | No of injections |
|---|---|---|---|
| Fixed monthly regimen | 8.5 | 8.0 | 11.7 vs 11.9 |
| As needed regimen | 6.8 | 5.9 | 6.9 vs 7.7 |

**Table 2:** Adverse events data for two years follow up.

| | Lucentis | Avastin | p value |
|---|---|---|---|
| All cause mortality | 2.8% | 2.9% | p=1.00 |
| Arterio-thrombotic events | 2.2% | 1.7% | p=0.68 |
| Stroke | 1.2% | 1.2% | p=1.00 |

**FUTURE**

I am open to the fact that efficacy findings of these two VEGF inhibitors for neovascular AMD may not transfer to patients with other conditions, such as RVO and DME, and that these drugs may behave differently for individual patients. CATT study proved that Avastin is non-inferior to Lucentis in wet AMD. [4] The onus is now on Lucentis to prove it's superiority over Avastin in other clinical scenarios requiring VEGF inhibition.

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**Glaucoma**

After cataract surgery the iridocorneal angle may become wider reducing the IOP somewhat.

**M Lateef Chaudhry**
**Editor-in-Chief**