AMD
Intravitreal injections: Drugs, Technique and Regimens
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Drugs
Drugs

- THE ERA OF CLINICAL PHARMACOTHERAPY FOR AMD is only slightly more than 10 years old.

- Pegaptanib sodium (Macugen; Pfizer, New York, New York, USA), approved in December 2004 and administered intravitreally at 6-week intervals prevented severe vision loss.
- It is an aptamer that selectively binds the vascular endothelial growth factor (VEGF) 165 isoform.
- However, Only about 6% of patients gained 3 or more lines of vision.
Drugs

- In July 2005, the American Society of Retina Specialists heard presentations of the Systemic Avastin for the Treatment of Neovascular AMD (SANA) trial as well as case reports of intravitreal bevacizumab use supported by optical coherence tomography (OCT) documentation.

Drugs

- Clinicians could obtain bevacizumab in 2005 and 2006 but were unable to use ranibizumab until weeks after FDA approval in June 2006.
Drugs

- With its easy availability, low cost, and suggested efficacy, intravitreal bevacizumab use for AMD expanded and multiple uncontrolled case series appeared in 2006 and 2007 with no obvious evidence of side effects or safety issues.

Drugs

- After FDA approval of ranibizumab in June 2006, many clinicians continued to use bevacizumab preferentially!
- Bevacizumab was used in nearly two-thirds of individual AMD patients treated with an anti-VEGF agent.
Drugs

- Bevacizumab is not a generic form of ranibizumab; ranibizumab and bevacizumab are different molecules produced in different cell culture systems.

Drugs

- Although both are murine-derived humanized monoclonal antibodies (-zumabs), the active binding site of ranibizumab has been affinity matured to produce stronger binding.
Drugs

- Bevacizumab (149 kDa) is larger than ranibizumab (48 kDa) and may not penetrate the retina as well.

- Because bevacizumab includes the Fc (constant region) of the immunoglobulin chain,
  - it may be a more potent antigenic stimulus
  - as well as persisting longer in blood if the molecule escapes the eye.
Drugs

- These observations may explain why Genentech chose to pursue clinical testing only on ranibizumab for intravitreal use.

Drugs

- Aflibercept (VEGF Trap-eye; Regeneron Pharmaceuticals, Tarrytown, New York, USA), a fusion protein with the second binding domain from VEGFR-1 and third binding domain from VEGFR-2 fused to the constant (Fc) region of human IgG1.
Drugs

- AMD clinical trials showed that 2 mg VEGF trap-eye injected either monthly or every other month was comparable to monthly dosing of ranibizumab in visual acuity gain and safety.

Avastin versus Lucentis

- An important question that needed to be addressed was whether there is any clinically relevant difference in efficacy and safety between the 2 agents when used on either a monthly or as-needed (pro re nata [PRN]) basis.
CATT Trial

Figure 1. The graph shows mean change in visual acuity score at month 12 in the Comparisons of Age-Related Macular Degeneration Treatments Trials Data from CATT Research Group, Martin DF, Maguire MG, et al. N Engl J Med 2011;364:1897–908.1

CATT Trial

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Difference in Mean Change in Visual Acuity Score (n of letters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab monthly</td>
<td>Ranibizumab monthly</td>
<td>-3.9</td>
</tr>
<tr>
<td>Bevacizumab as needed</td>
<td>Ranibizumab as needed</td>
<td>-4.1</td>
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<tr>
<td>Ranibizumab as needed</td>
<td>Ranibizumab monthly</td>
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<tr>
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<tr>
<td>Bevacizumab as needed</td>
<td>Ranibizumab monthly</td>
<td>-5.9</td>
</tr>
</tbody>
</table>

Figure 2. Graph showing Comparisons of Age-Related Macular Degeneration Treatments Trials results. Gray bars = 99.2% confidence intervals; dashed vertical lines = noninferiority limits of 5 letters. If the gray bars are within the noninferiority limits of the 5 letters, those treatments are equivalent. If the gray bar extends below the noninferiority limit, that treatment may be inconclusive. Reprinted with permission from CATT Research Group, Martin DF, Maguire MG, et al. N Engl J Med 2011;364:1897–908.3
Figure 4. Graph showing mean change in visual acuity at 1 year in the Comparisons of Age-Related Macular Degeneration Treatments Trials. SE = standard error. Reprinted with permission from CATT Research Group, Martin DF, Maguire MG, et al. N Engl J Med 2011;364:1897–908.3

Figure 3. Bar graph showing the absence of fluid on optical coherence tomography (OCT) at 1 year in the Comparisons of Age-Related Macular Degeneration Treatments Trials. Data from CATT Research Group, Martin DF, Maguire MG, et al. N Engl J Med 2011;364:1897–908.3
CATT Trial

- PRN ranibizumab is equivalent to ranibizumab given monthly at 1 year.
- Bevacizumab given monthly also is equivalent to ranibizumab given monthly at 1 year.
- PRN bevacizumab provides a visual acuity benefit, but 2-year data showed that PRN dosing of either drug was associated with less visual acuity gain than monthly dosing.
- Although there was no increased risk of arterial thrombotic events in the bevacizumab-treated patients, there was a statistically significant increase in serious systemic adverse events through 2 years.

Which agent?

- Q: Although anti-VEGF provides the cornerstone of treatment today for patients with neovascular AMD, challenges remain, such as which anti-VEGF agent to choose?
Which agent?

- The major factors are
  - cost,
  - efficacy,
  - safety,
  - and treatment burden.

Which agent?

- Patients in whom **cost** is an issue—e.g. they do not have insurance—are typically started on bevacizumab (**Avastin**) therapy.
Which agent?

- If they do well—and many, if not most, do—therapy is continued with the knowledge that we are probably going to have more of a treatment burden but at a far reduced cost.

Which agent?

- Whenever I initiate therapy in patients for whom cost is not an issue, I always discuss the available agents and many patients elect to go straight to the United States Food and Drug Administration (FDA)-approved agents.
Injection technique

Injection technique
Injection technique
Injection technique

Injection technique
Injection technique

Injection technique
Injection technique

- Pre- and Postoperative antibiotics??
- When is the First visit ??

Regimens and treatment protocols
AMD Treatment Protocols

- Monthly injections: standard of care
- Alternative individualized treatment strategies:
  - PRN (treat and observe)
  - PrONTO protocol (treat and observe).
  - Treat and extend or Inject and extend.

Monthly injection: is it a matter of cost?
Monthly injection: is it a matter of cost?

- Approximately 7 years after ranibizumab therapy in the ANCHOR or MARINA trials, one third of patients demonstrated good visual outcomes, whereas another third had poor outcomes.
- Compared with baseline, almost half of eyes were stable, whereas one third declined by 15 letters or more.
Monthly injection: is it a matter of cost?

- Even at this late stage in the therapeutic course, exudative AMD patients remain at risk for substantial visual decline.
Monthly injection: is it a matter of cost?

- Approximately one fifth of CATT patients developed GA within 2 years of treatment.
- Independent baseline risk factors included poor VA, RAP, foveal intraretinal fluid, monthly dosing, and treatment with ranibizumab.
- Anti-vascular endothelial growth factor therapy may have a role in the development of GA.

Loading dose? Do we need it?
Loading dose? Do we need it?

Individualized treatment
What is treat and extend?

- The dosing strategy consists of an initial induction or “loading” sequence of at least three initial monthly injections.
- If stable visual acuity, an absence of macular hemorrhage, and a dry OCT have been achieved at this point, patients continue to receive regular maintenance injections at increasing intervals.

What is treat and extend?

- At 6 weeks after the last of the 3 initial monthly injections, visual acuity, clinical findings, and OCT changes are recorded again, and patients receive an injection regardless of the presence or absence of disease activity.
What is treat and extend?

- However, the interval to the next visit (and scheduled injection) is based on an observed change in these parameters.
- If there are no changes, the next visit for examination and injection is scheduled for 8 weeks. If there is a change, the patient returns for another scheduled injection and examination after 4 weeks.

What is treat and extend?

- The observation and scheduled treatment interval is extended (hence the phrase “treat and extend”)
- 10 weeks and sometimes 12 weeks was chosen as the longest interval between office visits and treatments.
What is treat and extend?

- Baseline
- After 3 monthly (4 weeks) injections
- Extended to 6 weeks intervals
- Extended to 8 weeks intervals
- Extended to 10 weeks intervals
- Back to 8 weeks

What is treat and observe (PRN/PrONTO)

- This strategy does require monthly visits, clinical examinations, and OCTs. This means more frequent visits which is more burden on the patient (elderly) and their families and health care system.
What are the disadvantages of treat and observe (PRN/PrONGO)?

- Patients uncertain (and doctors too!) if or when they will need treatment?! And this may be a reason for some patients to skip visits!

What are the disadvantages of treat and observe (PRN/PrONGO)?

- Some patients managed with this strategy will return for assessments having already developed hemorrhages in the injection-free interval with irreversible vision loss!
What are the disadvantages of treat and observe (PRN/PrONTO)?

- You treat only when you see fluid!. Unlike DME and RVO, AMD is unforgiving disease! Each time fluid accumulates, this means CNV is growing and more photoreceptors loss!!

What are the disadvantages of treat and observe (PRN/PrONTO)?

- In theory, a dosing regimen that does not maintain the macula in a “dry” state could deny some patients the opportunity for further visual recovery!
What are the Advantages of Treat and Extend protocol?

- To put it in a nutshell: The “Treat and Extend” dosing regimen is a strategy intended to resolve macular exudation and maintain the macula in this “dry” state indefinitely with, when possible, fewer patient visits and treatments than monthly dosing.

What are the Advantages of Treat and Extend protocol?

- Reduction of treatment burden by reducing the number of patient visits and the number of imaging studies performed by eliminating the need for the monthly visits necessitated by alternative dosing strategies.
What are the Advantages of Treat and Extend protocol?

- Effective giving similar results to monthly injections but with fewer injections.

What are the Advantages of Treat and Extend protocol?

- Just as effective and even better than PrONTO protocol! Patients on a “treat and extend” dosing regimen receive a mandated injection at each visit, their eyes receive slightly more injections in 1st year, but a similar number of injections as received by patients who completed 24-month follow-up in the PrONTO study.
What are the Advantages of Treat and Extend protocol?

- The significant reduction in patient visits of nearly 50% without an increase in the number of treatments could potentially decrease the burden on patients, practitioners, and the healthcare system as a whole.

- Reduces the risk of new sight-threatening submacular hemorrhages (maintained VEGF suppression/more aggressive than PrONTO).

- Rare progression of GA overlying the neovascular lesions suggest additional long-term benefits of the “treat and extend” dosing regimen (less aggressive than monthly Rx).
What are the Advantages of Treat and Extend protocol?

- Patients and doctors are more compliant because both parties know when will be the next scheduled injection. No place for uncertainty!
- Patient will be less inclined to skip visits… because they know they will have an injection!

What are the Advantages of Treat and Extend protocol?

- You can know what is optimal injection free interval for each individual patient without macular exudation.
- Some patients could be 6 weeks, others 8 or 10 weeks.
Individualized Regimens: Treat and Extend Protocol

- Effective.
- Strict control of AMD.
- Practical to patient and doctor in every day practice.
- More compliance.
- Clear schedule.
- More Economic (less visits, injections and imaging).

PRN VA 0.4
PRN

RX and extend
Now on 12 weeks intervals VA 0.8
Refractory cases

- Double the dose
- Reduce treatment intervals to 2 weeks.
- Switch drugs or alternate drugs.
- Investigate the case again
  FFA+ICG? RAP/PCV
Refractory cases
Refractory cases

When to stop?
When to stop?

- The decision to stop anti-VEGF therapy in exudative AMD may occur in very different situations:
  - a **very positive situation** when the treatment is stopped because of the lasting resolution of exudation and vision stability,
  - or a situation **indicating failure** when discontinuation is attributable to the development of a fibrous macular disciform scar, chronic macular edema, macular atrophy, or a retinal or systemic complication

Conclusion
Conclusion

- Patients with AMD can be treated with either drugs starting on PRN basis with no compulsory loading dose but with strict follow up protocol and monitored extension.

Thank you....!