SWITCHING BETWEEN ANTI-VEGFs

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No financial interest in any product

The proven efficacy of anti-VEGF has resulted in millions of intravitreal injections (IVI).

In 2007 :800000 IVI ,but these numbers went up significantly

For example in USA :

-2009 :more than million
-2013: over 4 million
-2016: 5.9 million IVI

- What do we know about anti-VEGF therapy ?

-we know that Ranibizumab and Aflibercept are safe and effective

-we know that Bevacizumab (off-label) is safe and effective with outcomes similar to those seen with Ranibizumab

-we know that Pegaptanib is safe ,but compared with newer anti-VEGF drugs not as effective

-we know that Bevacizumab therapy is less expensive than the other therapies

-we know that the response to anti-VEGF therapy is variable

-we know that monthly and as needed treatment approaches for Bevacizumab and Ranibizumab yield similar outcomes

-we also know that treating at 3-months intrevals with Ranibizumab yields suboptimal outcomes

- What are some things we would like to know about anti-VEGF therapy ?

-we would like to know for how long we need to treat

-how infrequently we can treat and schedule visits yet achieve outcomes comparable with those of the registration trials

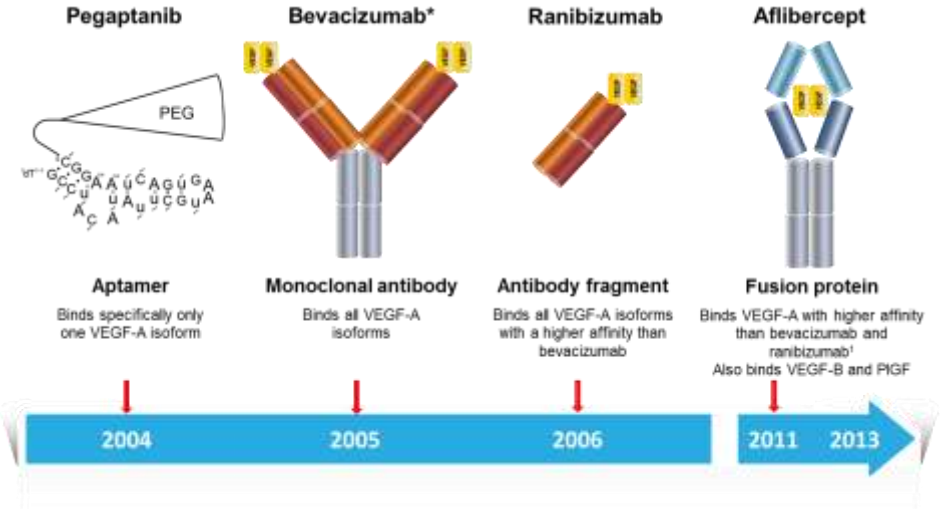
-we would like to know whether tachyphylaxis exists

-although the outcomes using the various drugs seem comparable for population ,we would like to know if there are individual patients who do better with one drug as opposed to one of the others

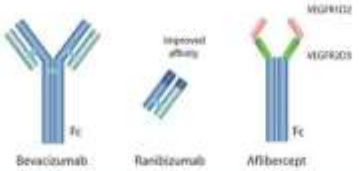
Switching anti-VEGF therapy

-why ?
-when ?

- Clinical researches have attempted to improve outcomes for patients by changing from one anti-VEGF drug to the other ,assuming a potential difference in activity and effect.
- Switching is performed following unsatisfactory treatment response ,most studies accept structural criteria on OCT rather than functional outcomes.
- Other considerations may also impact the decision to switch treatment ,for example, economic reasons.



Differences in Anti-VEGF agents



	Ranibizumab	Bevacizumab	Aflibercept
Molecule	Fab	Full –sized Mab	Fusion protein
Binds	VEGF -A	VEGF-A	VEGA-A, B and PlGF
Fc	No	Yes	Yes
Mol wt	48kDa	149kDa	115kDa
Intravitreal VEGF binding activity (Mathematical model)	30 days	27-38 days	83 days

- Following a switch of anti-VEGF agents ,there is a wide variation in clinical outcome

- The vast majority of studies in patients switching to Aflibercept from previous Ranibizumab/Bevacizumab treatment report a statistically significant reduction of retinal thickness on OCT ranging from 25-112 um.
- Complete success in terms of dry macula was reported in 15%-68%.

- In terms of V/A ,there are studies that reported statistically significant changes in V/A upon switching ,while others reported only anatomical changes without concomitant change in V/A.

- What conclusion can be drawn from the published data ?

1-Anatomical improvement with or without improvements in V/A are observed upon switching .

2-The relatively minor changes observed after switch are not clearly attributable to switching .

- Reasons for assuming that switching patients may lead to anatomical and /or functional improvements

1-There are large number of publications suggesting a structural and sometimes functional benefit .

2-Molecular and pharmacological differences between the agents result in different mechanism of action and are in keeping with the clinical benefit observed upon switching ;

-mode of action
-inherent resistance to the initial anti-VEGF agent
-drug tolerance -tachyphylaxis

3-The studies that show a lack of improvement report a mean outcome across a varied patient population ,there may be a subpopulation who are more likely to benefit from switching to an alternative anti-VEGF agent ,which may be masked within the reported patient population .

- Reasons for assuming that switching patients may not lead to functional and anatomical improvements

1-There is evidence that the biological and clinical efficacy of ranibizumab and aflibercept is equal ,that is ,there is no clinical difference between the 2 drugs.

-affinity and biological activity –evidence of equality
-equal outcome in clinical trials
-no clinical benefit was reported following a switch

2- Observed changes in clinical outcomes in uncontrolled studies may be attributable to other factors than switching ,such as natural change over time

-changes to patient responsiveness and treatment frequency
-disease responses are dynamic
-disease changes

3- Other confounding factors may create an incorrect conclusion of switch benefit in uncontrolled /retrospective studies

- Although there is no evidence for a generalized superiority of one drug over the other ,there might be a subset of patients with particular genetic (partial refractoriness) or pharmacodynamic(drug tolerance) characteristics for whom a drug switch may be beneficial .

- It is not possible to provide recommendations regarding a definitive time scale or clinical parameters when deciding whether switching or switching back would be appropriate .

- Future anti-VEGF switch


TABLE. Age-related Macular Degeneration and Diabetic Macular Edema Pipeline

THANK YOU