

ORAL MEDICATIONS FOR MS!

Gilenya and Aubagio

Champions against MS 4/20/13

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Oral Medications

- Since 2010, 3 new oral medications for MS:
 - Gilenya 2010
 - Aubagio 2012
 - Tecfidera 2013
- Opportunity to improve quality of life.
- But does new and/or oral = better for you?

Agenda

- **Aubagio**

- Mechanism of action, Metabolism
- Trial data
- Warnings, Adverse events

- **Gilenya**

- Mechanism of action, Metabolism
- Trial data
- Warnings, Adverse events

- **Is changing medications ok?**

- **How do I know when to switch?**

- **How do I pick the right drug for me?**

Aubagio

- 2nd oral drug for MS 2012
- Once-daily pill
- 7 mg or 14 mg
- Active metabolite of Arava
 - 1998 FDA-approved for rheumatoid arthritis
 - Though new for MS, there is 14 yrs experience in RA



Aubagio Mechanism of Action

- Exact mechanism of action not fully understood.
- Blocks an enzyme necessary for active production of new T and B cells.
- Old T and B cells can still be recycled.
- Immunosuppressive?

Aubagio Metabolism

- Eliminated via excretion into bile and/or urine.
- Can speed excretion by taking charcoal or cholestyramine.
 - If need to get off Aubagio, can clear in 11 days
- Without using charcoal or cholestyramine, Aubagio can remain in the body for up to 2 years.

Aubagio Phase III Trials

- TESMO: FDA approval based on this study
- TOWER
- TENERE

TESMO: Aubagio vs. placebo

	ARR	Risk of 3 month sustained disability	Risk of 6 month sustained disability
14mg Aubagio	31.2% reduction	29.8% reduction	No difference from placebo
7mg Aubagio	31.5% reduction	No difference from placebo	No difference from placebo
placebo	-----	-----	-----

TOWER: Aubagio vs. placebo

	ARR	Risk of 3 month sustained disability
14mg Aubagio	36.3% reduction	31.5% reduction
7mg Aubagio	22.3% reduction	No difference from placebo
placebo	-----	-----

TENERE: Aubagio vs. Rebif

- Endpoints:
 - Annualized relapse rate
 - Occurrence of relapse
 - Drug discontinuation
- **No significant** difference between 14mg Aubagio and Rebif for any of the endpoints.
- 7mg Aubagio performed **worse** than Rebif.

Take-Aways:

- Aubagio Dose: 7mg or 14mg?

14mg

- If your MS is not being well-controlled by a first-line MS drug:

Aubagio is not a good option for you.

Aubagio Black Box Warnings

Liver toxicity

Interference with normal fetal
development

Aubagio Warnings/Precautions

- Severe liver injury reported in Arava
- Screen liver blood tests in all patients
- Pregnancy excluded prior to start
- Patients counseled on serious fetal risk

If elevated liver blood tests, or pregnant or want to become pregnant:

Accelerated elimination procedure

Accelerated Elimination Procedure

- Cholestyramine 8 gms every 8 hrs x 11 days
- Oral activated charcoal powder 50 gms every 12 hours x 11 days
- At end of 11 days, 98% decrease in Aubagio blood concentration.

Aubagio Adverse events

Abnormal liver blood tests

Hair loss

Diarrhea

Flu

Nausea

Abnormal sensation/numbness/tingling

Drug Interactions

- ALWAYS tell your neurologist ALL the drugs you are taking.
- Aubagio may increase blood levels of:
 - Some diabetes medications
 - Oral contraceptives
- Warfarin (Coumadin): Aubagio decreases INR
- May decrease levels of cymbalta, tizanidine and others

Gilenya

- First oral drug for MS 2010
- 0.5 mg orally once daily
- First in class
 - No other drugs like this on the market



Gilenya Mechanism of action

- Exact mechanism in MS unknown
- Sphingosine 1 phosphate (S1P) receptor blocker
 - Some T cells require S1P receptor to leave lymph nodes
 - When S1P receptor blocked, T cells remain in lymph nodes
- T cells not killed or destroyed.
- Memory T cells responsible for protection against repeat infections are not effected
- Immunosuppressive?

Gilenya metabolism

- Metabolized in liver
- Excreted in bowel and urine

Gilenya Phase III Trials

- FREEDOMS
- TRANSFORMS
- FREEDOMS II

FREEDOMS: Gilenya vs. Placebo

	ARR	Risk 3 month sustained disability	Risk 6 month sustained disability	Mean EDSS at 2 Years
1.25 mg Gilenya	60% reduction	32% reduction	30% reduction	Decreased 0.03
0.5 mg Gilenya	54% reduction	30% reduction	30% reduction	No change
placebo	-----	-----	-----	Increased 0.13

TRANSFORMS: Gilenya vs. Avonex

	ARR	Risk of 3 month sustained disability*	Mean EDSS at 1 Year
1.25mg Gilenya	38% reduction	No difference from Avonex	Decreased 0.11
0.5mg Gilenya	52% reduction	No difference from Avonex	Decreased 0.08
Avonex	-----	-----	Increased 0.01

*Trial only 12 months

FDA Safety Recommendations for Gilenya

- Updated **April 2012**:
 - After a death following 1st dose.
 - Included review of trial and post-marketing data.
- Gilenya now **contraindicated** in patients:
 - With certain pre-existing or recent (within last 6 months) heart conditions or stroke
 - Who are taking certain antiarrhythmic (heart) medications.

FDA recommendations on Gilenya

1st Dose Monitoring

- **ALL** patients starting Gilenya
- Monitored for signs of a slow heart rate for at least 6 hours after 1st dose
 - **Hourly** pulse and blood pressure measurement
 - **EKG** before dosing and at the end of observation
- In patients who are at higher risk for or who may not tolerate slow heart rate:
 - Time of monitoring extended past 6 hours
 - Including continuous monitoring overnight

Who are “high risk” patients?

- Develop severe slow heart rate after 1st dose
- With certain pre-existing conditions in whom slow heart rate may be poorly tolerated
- With certain heart rhythm abnormalities
- Receiving therapy with other drugs that:
 - Slow the heart rate
 - Alter the hearts electrical conduction

Gilenya Warnings/Precautions

- **Decrease in heart rate** and/or electrical heart conduction
→ 1st dose monitoring.
- **Infections:** Possible increased risk of infections.
- **Macular edema:** 0.4% of patients.
 - Can occur with or without visual symptoms.
 - Ophthalmologic evaluation before starting and 3-4 months later.
 - Patients with diabetes mellitus or a history of uveitis at higher risk.
- **Decrease in pulmonary function**
- **Liver effects:** follow with blood tests.
- **Pregnancy:** wait 2 months after stopping before trying to conceive.

Gilenya Adverse events:

Headache

Flu

Diarrhea

Back pain

Liver test elevations

Cough

Drug Interactions

- ALWAYS tell your neurologist ALL the drugs you are taking.
- Ketoconazole increases Gilenya levels.
- Gilenya contraindicated in patients taking certain heart medications
 - antiarrhythmic

Is changing MS medications ok?

- Yes
- BUT:
 - Not every available drug is suited for every individual.
 - Changes with your neurologist's advice and OK.

How do I know when to switch?

- Disease poorly controlled:
 - Multiple relapses on current medication
 - Multiple new enhancing lesions on MRI

or

- Current medication intolerable:
 - Side effects of current medication intolerable
 - You are skipping your medication with regularity

Which MS medication is for me?

- We don't know (yet).
- It depends...
 - Are you having relapses despite treatment?
 - Is your MRI worsening despite treatment?
 - Tysabri
 - Gilenya
 - Tecfidera
 - Are you stable but tired of injections?
 - Gilenya
 - Tecfidera
 - Aubagio (If done having kids)

Thank You

Questions?