ORAL MEDICATIONS FOR MS!

Gilenya and Aubagio

Champions against MS 4/20/13
Alexandra Goodyear, MD
Stanford University
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

<table>
<thead>
<tr>
<th></th>
<th>ARR</th>
<th>Risk of 3 month sustained disability</th>
<th>Risk of 6 month sustained disability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>14mg Aubagio</strong></td>
<td>31.2% reduction</td>
<td>29.8% reduction</td>
<td>No difference from placebo</td>
</tr>
<tr>
<td><strong>7mg Aubagio</strong></td>
<td>31.5% reduction</td>
<td>No difference from placebo</td>
<td>No difference from placebo</td>
</tr>
<tr>
<td>Placebo</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
</tbody>
</table>
TOWER: Aubagio vs. placebo

<table>
<thead>
<tr>
<th></th>
<th>ARR</th>
<th>Risk of 3 month sustained disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>14mg Aubagio</td>
<td>36.3% reduction</td>
<td>31.5% reduction</td>
</tr>
<tr>
<td>7mg Aubagio</td>
<td>22.3% reduction</td>
<td>No difference from placebo</td>
</tr>
<tr>
<td>placebo</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>ARR</th>
<th>Risk 3 month sustained disability</th>
<th>Risk 6 month sustained disability</th>
<th>Mean EDSS at 2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.25 mg Gilenya</strong></td>
<td>60% reduction</td>
<td>32% reduction</td>
<td>30% reduction</td>
<td>Decreased 0.03</td>
</tr>
<tr>
<td><strong>0.5 mg Gilenya</strong></td>
<td>54% reduction</td>
<td>30% reduction</td>
<td>30% reduction</td>
<td>No change</td>
</tr>
<tr>
<td>placebo</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>Increased 0.13</td>
</tr>
</tbody>
</table>
# TRANSFORMS: Gilenya vs. Avonex

<table>
<thead>
<tr>
<th></th>
<th>ARR</th>
<th>Risk of 3 month sustained disability*</th>
<th>Mean EDSS at 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25mg Gilenya</td>
<td>38% reduction</td>
<td>No difference from Avonex</td>
<td>Decreased 0.11</td>
</tr>
<tr>
<td>0.5mg Gilenya</td>
<td>52% reduction</td>
<td>No difference from Avonex</td>
<td>Decreased 0.08</td>
</tr>
<tr>
<td>Avonex</td>
<td>-----</td>
<td>-----</td>
<td>Increased 0.01</td>
</tr>
</tbody>
</table>

*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 1\textsuperscript{st} 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 → 1\textsuperscript{st} 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?