Direct Comparison of Apremilast and Best Supportive Care Using a Discrete Event Simulation

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DIRECT COMPARISON OF APREMILAST AND BEST SUPPORTIVE CARE USING A DISCRETE EVENT SIMULATION

Zoe Clancy, PharmD
OUTLINE

- Psoriatic Arthritis Disease Brief
  - Mechanism of action
  - Differences between Psoriatic Arthritis and Rheumatoid Arthritis
  - Current treatment

- Discrete Event Simulation
  - Definition
  - Model Overview
  - Model Results
Psoriatic Arthritis Disease Brief
PsA is a Chronic Inflammatory Disease of the Joints and Skin Resulting from an Uncontrolled Immune Response

Over-production of TNF-α as well as other cytokines, alters bone homeostasis, resulting in the joint damage seen in PsA

PsA differs from Rheumatoid Arthritis (RA) based on the presence of psoriatic-associated conditions and the distribution and appearance of the affected joints.

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>PsA</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriatic skin lesions present</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td>Psoriasis-associated nail symptoms</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td>Distribution of affected joints</td>
<td>Often asymmetrical</td>
<td>Symmetrical</td>
</tr>
<tr>
<td></td>
<td>Various joints affected</td>
<td>Primarily involving hands and wrists</td>
</tr>
<tr>
<td>Appearance of the affected joint</td>
<td>More generalized swelling</td>
<td>Pronounced swelling over joints</td>
</tr>
<tr>
<td></td>
<td>Produce a sausage-like appearance in fingers or toes</td>
<td>(RA nodules)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>Variable</td>
<td>Predictable</td>
</tr>
<tr>
<td>Rheumatoid factor status</td>
<td>Seronegative</td>
<td>Seropositive</td>
</tr>
</tbody>
</table>

In 75% of cases, psoriasis precedes the joint disease.

In 15% of cases, the onset of skin disease is at the same time as onset of joint involvement.

In 10% of cases, the joint disease precedes the psoriasis.
PsA and QoL

- For people with psoriatic arthritis, quality of life is impacted by both the physical symptoms of the disease and the emotional burden of sometimes disfiguring skin symptoms.
- Compared to rheumatoid arthritis and ankylosing spondylitis, people with psoriatic arthritis report more psychosocial problems.
- This finding fits with data from a survey of people with psoriasis, which found that 75 percent of patients believe the skin condition had a moderate to large negative impact on their quality of life, with alteration in their activities and work.

PsA has a significant negative impact on health-related quality of life (HRQoL)

- Decreased QoL as measured by the Medical Outcomes Short-Form 36 Questionnaire (SF-36) scores in patients with PsA compared to the general population.¹
- 19% of patients with PsA claimed their disease resulted in “marked physical limitations”.²
- 8.2% of patients sought assistance for home activities from friends or family.³
- Both physical functioning and emotional well-being are decreased.
- In patients with PsA and psoriasis:
  - Arthritis component - greater impact on physical functioning
  - Psoriasis component - greater impact on emotional well-being
    - Skin lesions associated with poor self-image and distress from pruritus and pain.

Epidemiology

Prevalence 5% - 40% of people with psoriasis

Race Affects Caucasians more than other races

Gender Men and women equally affected

Age of onset 40–50 years of age, can occur earlier

TREATMENT OPTIONS

Mild Disease
- NSAIDs

Moderate to Severe Disease
- Corticosteroids
- Traditional DMARDs
  - MTX
  - Sulfasalazine
  - Leflunomide
- Biologic DMARDs
National Guideline Recommendations in Patients with PsA

PsA Disease Status

- Mild
  - NSAIDs

- Moderate/Severe*
  - DMARDs
    - Leflunomide
    - Sulfasalazine
  - TNF inhibitors
    - Adalimumab
    - Etanercept
    - Infliximab

*No evidence supporting DMARDs ahead of TNF inhibitors (effect size: TNF inhibitors > traditional DMARDs). However, TNF inhibitors are recommended for patients who fail to respond to at least one DMARD therapy unless poor prognosis present.

Grade A=Based on evidence from meta-analysis of randomized controlled trials (RCT) or ≥ 1 RCT

Adverse Effects Limit the Benefits of Therapy with Traditional Systemic DMARDs and Biologics

**Traditional systemic agents**
- Methotrexate (MTX) has weak and conflicting evidence in the management of PsA with risks of serious toxic reactions.
- MTX is not approved by the FDA
- Leflunomide does not have FDA approval and requires monitoring for hepatic toxicity
- Sulfasalazine has limited evidence in the management of PsA with rarely occurring serious toxicities.

**Biologics**
- Mild injection-site/infusion reactions
- Black box warning of risk of serious infections and malignancies
  - Increased risk of infection
    - Overall infections, odds ratio 1.18 (95% confidence interval, 1.05-1.33)
  - Patients with PsA are at greater risk for mortality from infection.

The Significant Burden Associated with PsA

- **Patients with PsA:**
  - Suffer from limited mobility, pain, inflammation and stiffness as well as skin lesions from psoriasis
  - Have a poorer quality of life
  - Are less likely to be employed and less likely to be productive
  - Incur higher healthcare costs

- **New PsA therapies are needed that demonstrate:**
  - Effective Treatment in Patients with Active Psoriatic Arthritis
  - Improved Safety and Better Tolerability than Traditional DMARDS and Biologics
  - Patient Convenience over Injectable Biologics
  - Cost savings compared to Biologics
Apremilast is a first-in-class PDE4 inhibitor

- MOA: modulates pro-inflammatory and anti-inflammatory mediators
- Administration: oral and does not need dose adjustments

This drug represents a novel treatment option for patients and can represent a delay in biologic therapy\textsuperscript{14}

OUTCOME MEASURES OF PsA

- ACR response criteria: 20%, 50%, 70% (validated in RA, not PsA)
  - Tender and swollen joint count (modified for PsA to include DIP and CMC joints: 78/76, 68/66)
  - 3/5: patient global, physician global, patient pain, HAQ, acute phase reactant (sed rate, CRP)

- Psoriatic Arthritis Response Criteria (PsARC)
  - Improvement in at least 2 of 4 criteria, including:
    - Physician global assessment (0–5)
    - Patient global assessment (0–5)
    - Tender joint score (≥ 30%)
    - Swollen joint score (≥ 30%)
  - Improvement in at least 1 of 2 joint scores
  - No worsening in any criteria
DISCRETE EVENT SIMULATION
All Models Are Wrong, But Some Are Useful

-George E.P. Box
**Discrete Event Simulation (DES)**

- DES is a modeling technique that is event-based

**Advantages vs Markov Models**

- DES can incorporate new data as it becomes available

- Can use an individual patient’s values and examine the decision from his or her point of view

- Can capture multiple events with competing risks
Patients with active psoriatic arthritis who have failed methotrexate (MTX) therapy will be split into two groups: apremilast followed by best supportive care (BSC) and patients only receiving BSC.
**Step 1: Create Patients and Assign Characteristics**

- **Assign Baseline Utilities:**
  - Age
  - Gender (45% male)
  - Life expectancy
  - Mortality
**Step 2: Patients enter either APR or BSC Treatment Arm**

- If ‘Is Patient starting a Trial?’ is TRUE, then patients enter APR arm
- ‘Assign Time to Event TP’ sets the next event to death and logs the time at the beginning of the time-to-event period
- Time advances in “Wait Next Event TP”
Step 2: Patients enter either APR or BSC treatment arm

- Patients move to ‘Assign QALYs and Costs TP’ where QALYs and Costs are calculated
- The VBA module is used to calculate Other Healthcare Costs
  - The VBA module computes the patient’s age each month and tallies the costs over the course of the period
Step 2: Patients enter either APR or BSC treatment arm

- After costs and QALYs have been assigned, 'Death in TP?' checks to see if the time of death event was prior to the end of the Trial Period.

- If so, patient is disposed of in the model, otherwise patient continues to BSC.
**Step 3: Decide if Treatment was Effective (or Not)**

- Patients enter a decision module (‘DECIDE outcome of Trial Period’) which decides whether the patients achieved a PsARC score (effective treatment) or not.
- If treatment effective, patients are assigned to a PASI group to allocate future costs and QALYs.
- Patients who are not successfully treated move to the BSC arm.
**Step 3: Decide if Treatment was Effective (or not)**

- ‘Assign Time to Event PASI’ module assigns a length of time until patients move to BSC
- Similar to the Trial Period arm, patient is advanced in time through the ‘Wait Next Event PASI’ module to the sooner of either Death or BSC or model end
- Costs and QALYs are assigned as in Trial Period arm
**Step 4: BSC, Death, or Model End**

- Patients enter BSC arm either at beginning of the model run or through discontinuation of treatment.
- Similar to Trial Period and Apremilast Arm, with patients disposed of at the end.
- The Excel read/write modules are also shown.
**Model Assumptions**

- Patients who enter the BSC arm do not go back to apremilast therapy
- There are no changes to BSC or treatment paradigms of PsA in clinical practice over the time horizon of the model (5 years)
- The population to which the model is applied to follows the age and life expectancy of that in the model
- HAQ scores return to baseline after discontinuation of treatment
- No monitoring or lab costs for apremilast
**Model limitations**

- Data was sourced from clinical trials and not real world

- PASI is used as the trial period endpoint, but is not the clinical trial endpoint for efficacy

- Indirect costs of treatment are not accounted for in the model
## Model results

<table>
<thead>
<tr>
<th>Rep</th>
<th>Control Costs</th>
<th>Control QALYs</th>
<th>Apremilast Costs</th>
<th>Apremilast QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>$30,558.54</td>
<td>19.70</td>
<td>$288,081.27</td>
<td>34.00</td>
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<td>2.00</td>
<td>$107,698.74</td>
<td>53.81</td>
<td>$162,649.05</td>
<td>54.36</td>
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<td>3.00</td>
<td>$66,412.11</td>
<td>36.19</td>
<td>$302,328.11</td>
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<td>4.00</td>
<td>$139,131.43</td>
<td>68.18</td>
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<tr>
<td>5.00</td>
<td>$32,584.15</td>
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<td>$128,977.00</td>
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<tr>
<td>6.00</td>
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<td>7.00</td>
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<td>9.00</td>
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<td>10.00</td>
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<tr>
<td>11.00</td>
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<td>$504,847.20</td>
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<td>13.00</td>
<td>$103,474.64</td>
<td>50.81</td>
<td>$123,192.79</td>
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<td>14.00</td>
<td>$73,509.76</td>
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<td>15.00</td>
<td>$113,050.81</td>
<td>64.10</td>
<td>$246,031.07</td>
<td>65.72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>QALY/patient</th>
<th>Cost/patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markov Model</td>
<td>0.29</td>
<td>$41,338</td>
</tr>
<tr>
<td>DES</td>
<td>0.86</td>
<td>$33,888</td>
</tr>
</tbody>
</table>

Comparison of DES to Markov Model

- Model cost results are within 20%
CONCLUSIONS

- DES models are more adaptable, compared to Markov models
  - Once data becomes available, for example QOL instrument data, the DES is easily updated

- DES and Markov models share limitations, specifically the availability and quality of data
  - Markov models have less data requirements

- A comparison of two models with the same data shows differences that can be attributed to
  - time to event that was used to calculate drop off to BSC
  - distributions used for age and life expectancy
REFERENCES