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\textsuperscript{1}

Over-production of TNF-\(\alpha\) as well as other cytokines, alters bone homeostasis, resulting in the joint damage seen in PsA\textsuperscript{4}

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</td>
<td>(RA nodules)</td>
</tr>
<tr>
<td></td>
<td>appearance in fingers or toes</td>
<td></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>

Key Concepts

- 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.
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 family³
- 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.

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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)^2
    - 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
PREMILAST

- 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

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 ($\geq 30\%$)
    - Swollen joint score ($\geq 30\%$)
  - 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

## Comparison of DES to Markov Model

- Model cost results are within 20%

<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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<tr>
<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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<tr>
<td>3.00</td>
<td>$66,412.11</td>
<td>36.19</td>
<td>$302,328.11</td>
<td>48.89</td>
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<tr>
<td>4.00</td>
<td>$139,131.43</td>
<td>68.18</td>
<td>$651,137.37</td>
<td>74.52</td>
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<tr>
<td>5.00</td>
<td>$32,584.15</td>
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<td>6.00</td>
<td>$86,104.37</td>
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<td>7.00</td>
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<td>38.87</td>
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<td>8.00</td>
<td>$94,376.35</td>
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<td>$198,235.75</td>
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<tr>
<td>9.00</td>
<td>$99,138.22</td>
<td>53.90</td>
<td>$224,178.43</td>
<td>60.20</td>
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<tr>
<td>10.00</td>
<td>$96,838.01</td>
<td>57.71</td>
<td>$226,460.36</td>
<td>59.30</td>
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<tr>
<td>11.00</td>
<td>$75,393.11</td>
<td>41.54</td>
<td>$210,705.91</td>
<td>48.16</td>
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<tr>
<td>12.00</td>
<td>$106,148.80</td>
<td>55.74</td>
<td>$504,847.20</td>
<td>60.29</td>
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<tr>
<td>13.00</td>
<td>$103,474.64</td>
<td>50.81</td>
<td>$123,192.79</td>
<td>51.13</td>
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<tr>
<td>14.00</td>
<td>$73,509.76</td>
<td>37.78</td>
<td>$142,757.01</td>
<td>38.63</td>
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<tr>
<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>

Total Costs: $1,299,567.67, 692.65, $3,841,176.07, 757.51
Avg/Patient Costs: $17,327.57, 9.24, $51,215.68, 10.10
Avg: $33,888.11, 0.86
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