Optimal Treatment of Knee Monarthritis in Juvenile Idiopathic Arthritis: A Decision Analysis

TIMOTHY BEUKELMAN,1 JAMES P. GUEVARA,2 AND DANIEL A. ALBERT3

Objective. To identify the optimal initial treatment strategy for knee monarthritis in juvenile idiopathic arthritis (JIA) using a decision model and parents’ preferences.

Methods. We utilized a decision analysis model with Markov states and a 6-month multi-attribute outcome with 7 dimensions pertinent to the treatment decision. The 3 most common treatment strategies for knee monarthritis were compared: nonsteroidal antiinflammatory drugs (NSAIDs) only, NSAID trial followed by intraarticular corticosteroid injection (IACI) if arthritis was not resolved after 2 months, and initial IACI. Probability estimates for the efficacy and adverse effects of NSAIDs and IACIs were derived from a systematic review of the literature. Parents’ preferences for the 7 dimensions of the multi-attribute outcome were elicited by a unique hybrid of the time tradeoff and magnitude estimation techniques. These preferences were then combined with the outcomes of the decision analysis to determine an individual’s preferred treatment.

Results. The NSAID trial strategy may avert IACIs in some patients, but at a cost of continued active arthritis. The number of patients that need to be treated with the NSAID trial strategy to avoid a single IACI compared with the initial IACI strategy is 3.8 with an expected additional cost of 6.7 months of active arthritis. Of the 12 parent subjects, 11 (92%) preferred the initial IACI strategy and 1 preferred the NSAID-only strategy. These preferences were not sensitive to model assumptions or probability estimates.

Conclusion. Initial IACI appears to be the optimal treatment strategy for knee monarthritis in JIA.

INTRODUCTION

Knee monarthritis is a common and important manifestation of juvenile idiopathic arthritis (JIA). It is the most common initial presentation of the oligoarthritis subtype (1), which accounts for up to 50% of all cases of JIA (2,3). Knee monarthritis may also occur during the course of any of the subtypes of JIA. Childhood arthritis that involves few joints may still have a prolonged course and result in considerable morbidity, including joint erosions and leg length discrepancy (1,4–6).

The optimal treatment for knee monarthritis in JIA is not known. Both nonsteroidal antiinflammatory drugs (NSAIDs) and intraarticular corticosteroid injections (IACIs) are effective (7). Many authors recommend treatment with a trial of NSAIDs followed by IACI if the arthritis does not improve (2,7), although to our knowledge, this treatment strategy has not been specifically studied. Results from a physician questionnaire survey regarding the initial treatment of knee monarthritis showed that 46% of pediatric rheumatologists recommend NSAIDs for up to 2 months before IACIs. By contrast, 27% recommend initial IACIs without a preceding NSAID trial, and 21% recommend a NSAID trial of 2–6 months before increasing therapy (8).

Choosing among treatment strategies involves a tradeoff of several different outcome dimensions, such as duration of arthritis, the associated potential for long-term complications, adverse effects of therapies, and the discomfort of daily medications or potentially painful procedures. These dimensions are separate and not easily compared and evaluated, making the results of a typical clinical trial difficult to interpret (9).

Decision analysis is a quantitative approach ideally suited to compare clinical strategies under conditions of uncertainty and complex tradeoffs (10,11). This approach often utilizes a decision tree model to represent the clini-
cal scenario with the outcomes of different clinical strategies. Model complexities, such as patients transitioning from one clinical state to another over time, can be represented with Markov models or other methods (12,13). Probabilities for the events in the model are typically derived from best estimates in the published literature to the extent that this is possible (11). Complex outcomes and tradeoffs in decision analyses have been modeled with multi-attribute outcomes that capture the different dimensions of clinical decisions (14,15). Preference assessment methods can be used to determine relative or absolute values for different health states or dimensions of a multi-attribute outcome (16,17). Therefore, decision analysis makes the tradeoffs of treatment decisions explicit and may better elucidate the optimal treatment strategy for knee monarthritis in JIA.

We designed and analyzed a decision tree utilizing Markov models for the initial treatment of knee monarthritis in JIA to determine the 6-month multi-attribute outcomes for the 3 most common treatment strategies practiced by pediatric rheumatologists. Over 90% of pediatric rheumatologists treat knee monarthritis in JIA with 1 of these 3 strategies (8). The decision tree model was constructed and analyzed with TreeAge Pro Suite software (TreeAge Software, Williamstown, MA). A 1-month cycle length and 6-month total time horizon were used. A simplified version of the decision tree model is shown in Figure 1.

Each of the 3 treatment strategies was represented by a Markov decision analysis model that compared 3 treatment strategies: NSAIDs alone for 6 months, NSAIDs followed by IACI in cases of poor response after 2 months, and initial IACI. In the case of relapse of arthritis, the treatment type (NSAID or IACI) was again determined by their particular strategy. Patients in a treatment state could experience minor or major medication adverse effects with each cycle. Minor adverse effects were defined as gastrointestinal (GI) upset for NSAIDs and hypopigmentation for

**MATERIALS AND METHODS**

**Model structure and assumptions.** We developed a Markov decision analysis model that compared 3 treatment strategies: NSAIDs alone for 6 months, NSAIDs followed by IACI in cases of poor response after 2 months, and initial IACI. Over 90% of pediatric rheumatologists treat knee monarthritis in JIA with 1 of these 3 strategies (8). The decision tree model was constructed and analyzed with TreeAge Pro Suite software (TreeAge Software, Williamstown, MA). A 1-month cycle length and 6-month total time horizon were used. A simplified version of the decision tree model is shown in Figure 1.

Each of the 3 treatment strategies was represented by a Markov model with 3 possible health states: active arthritis with NSAID treatment, active arthritis with IACI treatment, and resolved arthritis. All simulated patients entered the model with active arthritis and the treatment type determined by their chosen treatment strategy. Patients who responded to treatment assumed the resolved arthritis state in the next cycle. Resolved arthritis could remain resolved or relapse back to active with each subsequent cycle. In the case of relapse of arthritis, the treatment type (NSAID or IACI) was again determined by their particular strategy. Patients in a treatment state could experience minor or major medication adverse effects with each cycle. Minor adverse effects were defined as gastrointestinal (GI) upset for NSAIDs and hypopigmentation for...
IACIs. Major adverse effects were defined as significant GI bleeding or kidney complications for NSAIDs and septic arthritis for IACIs.

Several model assumptions were made regarding the use and effectiveness of NSAIDs and IACIs. Patients in the NSAID-only strategy received a new class of NSAIDs after each 2 month period of ineffective treatment (up to 3 different NSAIDs in the 6-month time horizon). Each new NSAID tried at 2 month intervals was assumed to have the base-case probability of success, regardless of previous NSAID therapy (18). NSAIDs were discontinued immediately following resolution of arthritis. Resolved arthritis was assumed to have the same probability of recurrence following treatment with either NSAIDs or IACIs. In cases of major NSAID adverse effects, NSAIDs were discontinued and the patient received IACIs. Patients in the NSAID trial strategy received NSAIDs as in the NSAID-only strategy, except that they received IACIs if the arthritis was not resolved after 2 months of NSAIDs. Patients in the initial IACI strategy did not receive NSAIDs unless they had active arthritis following 2 IACIs in the 6-month time horizon or a major IACI adverse effect. Patient sedation was not modeled as part of the IACI procedure. The probability of remaining in the resolved arthritis state was assumed to decrease linearly from month 1 to month 6 following IACIs, based on the survival curves from several studies (19–23). In NSAID treatment cycles that resulted in resolution of arthritis, the duration of arthritis for that cycle was assumed to be 0.5 months (half-cycle correction) based on a reported mean time to favorable response with NSAID treatment of 34 days (24). In IACI treatment cycles that resulted in resolution of arthritis, the duration of arthritis for that cycle was assumed to be 0.07 months (2 days) based on a nearly immediate response to IACI (25,26).

**Multi-attribute outcome.** A decomposed multi-attribute outcome was chosen due to the complexity of the treatment decision, the fact that utilities have not been established for the various health states in JIA, and the difficulties inherent in measuring utilities for brief experiences such as the IACI procedure (27). It was assumed that parents’ preferences for the dimensions of the treatment outcome would differ. A decomposed multi-attribute outcome allowed for the consideration of such differences. The use of decomposed multi-attribute methods to describe health states is well established (17,28), and multi-attribute decision analysis models have been utilized for other medical decisions with complex tradeoffs (14,15). The multi-attribute outcome of the model had 7 dimensions: cumulative duration of active arthritis, cumulative duration of daily oral NSAID medication, number of IACIs received, number of months with minor NSAID adverse effects, number of IACI minor adverse effects, number of major NSAID adverse effects, and number of major IACI adverse effects. All models were analyzed using 1 million first-order Monte Carlo microsimulations for each treatment strategy (29), and the mean expected values for each dimension of the multi-attribute outcome are reported.

**Model probability estimates.** The model probabilities were derived from the published literature. A structured Medline search was performed for all English-language articles from 1966 to 2006. The following medical subject headings terms were used: “arthritis, juvenile rheumatoid,” “anti-inflammatory agents, non-steroidal,” “injections, intra-articular,” and “adverse effects.” The reference sections of all identified articles, as well as standard pediatric rheumatology textbooks, were searched to ensure that no important publications were omitted. Published abstracts that were referenced by identified articles or textbooks were considered. All publications that appeared to assess the efficacy or adverse effects of NSAIDs or IACIs in childhood arthritis were obtained and reviewed further. Studies of adult subjects were included in estimating the probability of NSAID and IACI major adverse effects due to insufficient data in children. Studies of aspirin were excluded. To estimate IACI effectiveness, only studies of triamcinolone hexacetonide were included, given its demonstrated superiority over other corticosteroids (19–21). In estimating the effectiveness of NSAIDs and IACIs, the outcome of interest was the proportion of subjects whose arthritis resolved by subjective or objective measures.

As anticipated, significant heterogeneity of study designs, subject populations, treatment regimens, and outcome measures did not permit formal meta-analysis. Rather, ad hoc aggregation was performed with all attempts to use the most reliable and relevant data. Preference was given to studies with larger sample sizes, prospective designs, resolution of arthritis as the outcome measure, subjects who had active arthritis in 1 or only a few joints, and subjects who did not receive other medications concurrently. The base-case probabilities were determined by weighted averages from the most relevant studies. The minimum and maximum values for the probability estimates were determined from the 95% confidence intervals of a binomial distribution of the weighted averages and the probability extremes found in the individual selected publications.

**Preference assessment.** Following approval by the Institutional Review Board, subjects were recruited sequentially from a convenience sample of parents of children diagnosed with oligoarthritis visiting the rheumatology clinic as part of their usual care. The data were gathered by one investigator (TB) in a structured interview using a visual aid designed for this study. Responses were recorded on a standard form.

Each dimension of the multi-attribute outcome was valued in arthritis equivalents using a unique hybrid of the time tradeoff and magnitude estimation techniques (30,31). After hearing a short description of each dimension (Table 1), subjects were asked to choose if they would rather their child experience active arthritis of the knee for 1 month or the dimension being evaluated. Based on the response, the duration of active arthritis was systematically increased or decreased until a point of indifference between active arthritis and the dimension being evaluated was identified. The arthritis equivalent value for each dimension was considered equal to this duration of arthritis
tis at the indifference point. The lower limit for arthritis equivalent values was set at 0.03 months (1 day) and the upper limit was set at 1200 months (100 years). After all dimensions were evaluated, the responses were reviewed, and subjects were allowed to revise their responses if desired. The following patient information was obtained: age at onset of arthritis, current age, and history of previous IACI and NSAID treatment and adverse effects.

Determination of optimal treatment. For each of the 3 treatment strategies, the mean expected value for each dimension (derived from the decision model) was multiplied by the respective arthritis equivalents value (derived from the preference assessment) for each individual subject. For example, if 0.94 IACIs were expected for a given treatment strategy according to the probability model, and the discomfort of the IACI procedure was equal to 0.23 months of arthritis according to the preference assessment, then the number of IACIs dimension contributed 0.22 months of arthritis equivalents to that given treatment strategy. The resulting products for each of the 7 dimensions were then summed to generate the total expected arthritis equivalents value for each treatment strategy. The optimal treatment strategy for each individual subject was therefore the one with the lowest arthritis equivalents value.

Sensitivity analyses. Extensive sensitivity analyses were performed. The extremes of effectiveness and probabilities of adverse effects were evaluated in all 4 possible combinations of maximal and minimal benefits of treatment with NSAIDs and IACIs. The effects of continuing NSAIDs after resolution of arthritis with a resultant zero possibility of arthritis recurrence (unless NSAIDs were discontinued due to major adverse effects) were evaluated for all models. In a separate analysis to evaluate the effect on subjects’ optimal treatment strategies, the duration of the NSAID trial was decreased from 2 months to 1 month.

RESULTS

Probability estimates. The probability estimates and ranges used in sensitivity analysis are presented in Table 2. Initial resolution of arthritis shortly after IACI was almost universal in the studies that reported this outcome. Continued resolution of knee arthritis 6 months following IACI was more variable (range 56–85%). The probability of resolution of arthritis with NSAID therapy was ~16% (range 7–35%) for each 2-month period. Hypopigmentation following IACI was very uncommon, particularly for the knee. GI upset during NSAID treatment was relatively common, although estimates varied depending on the definition and method of identification. As expected, major adverse effects for both treatments were rare.

<table>
<thead>
<tr>
<th>Event</th>
<th>P (range)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of arthritis 1 month post-IACI</td>
<td>0.99 (0.90–0.999)</td>
<td>(20, 25, 32)</td>
</tr>
<tr>
<td>Resolution of arthritis 6 months post-IACI</td>
<td>0.73 (0.56–0.85)</td>
<td>(20, 22, 25, 26, 32–34)</td>
</tr>
<tr>
<td>Resolution of arthritis with 1st month of NSAIDs</td>
<td>0.05 (0.02–0.15)</td>
<td>(35–39)</td>
</tr>
<tr>
<td>Resolution of arthritis with 2nd month of NSAIDs</td>
<td>0.12 (0.05–0.24)</td>
<td>(30, 40–42)</td>
</tr>
<tr>
<td>IACI minor AE (per injection)</td>
<td>0.013 (0.006–0.024)</td>
<td>(22, 23, 32, 34, 43–47)</td>
</tr>
<tr>
<td>NSAID minor AE (per month)</td>
<td>0.15 (0.05–0.25)</td>
<td>(37, 41, 42, 48–68)</td>
</tr>
<tr>
<td>IACI major AE (per injection)</td>
<td>0.00002 (0.000002–0.00007)</td>
<td>(69–73)</td>
</tr>
<tr>
<td>NSAID major AE (per month)</td>
<td>0.00009 (0.00002–0.00014)</td>
<td>(68, 74–78)</td>
</tr>
</tbody>
</table>

* IACI = intraarticular corticosteroid injection; NSAIDs = nonsteroidal antiinflammatory drugs; AE = adverse effect.
Model outcomes. The 6-month multi-attribute outcomes for the base-case model and the extreme values from sensitivity analyses are shown in Table 3. As expected, the NSAID-only treatment strategy resulted in the longest duration of arthritis and the greatest exposure to NSAIDs and their associated adverse effects. The initial IACI treatment strategy resulted in the shortest duration of arthritis and the greatest exposure to IACIs and their associated adverse effects. The NSAID trial treatment strategy resulted in dimension values between these 2 extremes. In sensitivity analysis, the amount of arthritis expected in the worst-case scenario for initial IACI is less than one-third that for the best case of either of the 2 other treatment strategies.

The NSAID trial treatment strategy results in fewer IACIs than the initial IACI treatment strategy, at the cost of a greater expected duration of arthritis. Using the base-case results, 3.8 patients needed to be treated with the NSAID trial strategy to avoid 1 IACI. However, each of these patients experienced a mean of an additional 1.75 months of arthritis for each IACI avoided compared with the initial IACI treatment strategy. When maximum NSAID effectiveness and minimum IACI effectiveness were assumed in the model, the number of patients who needed to be treated with the NSAID trial strategy to avoid 1 IACI was lowered to 1.6 patients, with a total of 2.2 months of additional active arthritis for each IACI avoided.

Even when assuming maximal NSAID effectiveness, most patients (64%) in the NSAID trial treatment strategy failed to attain resolution of arthritis at 2 months and consequently underwent at least 1 IACI in the 6-month period.

Assessment of preference. Of the 13 subjects identified, 12 agreed to participate. No subject reported difficulty with understanding or completing the preference assessment task. The subjects’ children had a median age of 8 years and an onset of arthritis a median of 3 years prior. Four children had extended oligoarthritis and 8 had persistent oligoarthritis. All 12 children had undergone at least 1 IACI, and 11 had received scheduled NSAIDs. Four children had experienced hypopigmentation associated with IACIs, and 2 experienced stomachache associated with NSAIDs. No children had experienced a major adverse effect of IACIs or NSAIDs.

The resulting arthritis equivalent values for the dimensions of the multi-attribute outcome as elicited by preference assessment are shown in Table 4. Most subjects (75%) felt that having their child undergo the discomfort of IACI was preferable to 0.5 months or more of active arthritis. Even when assigning maximal NSAID effectiveness, most patients (64%) in the NSAID trial treatment strategy failed to attain resolution of arthritis at 2 months and consequently underwent at least 1 IACI in the 6-month period.

### Table 3. Six-month multi-attribute outcomes for the 3 treatment strategies*

<table>
<thead>
<tr>
<th>Dimension</th>
<th>NSAIDs only</th>
<th>NSAID trial</th>
<th>Initial IACI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months of arthritis</td>
<td>4.8 (3.5–5.5)</td>
<td>2.0 (1.8–2.3)</td>
<td>0.25 (0.16–0.54)</td>
</tr>
<tr>
<td>Number of IACI</td>
<td>0.004 (0.0006–0.006)</td>
<td>0.94 (0.69–1.2)</td>
<td>1.2 (1.1–1.4)</td>
</tr>
<tr>
<td>Months of NSAID</td>
<td>5.0 (3.9–6.0)</td>
<td>2.0 (1.9–3.4)</td>
<td>0.01 (0.005–0.13)</td>
</tr>
<tr>
<td>Number of IACI minor AE</td>
<td>0.00005 (0.000004–0.00002)</td>
<td>0.01 (0.004–0.03)</td>
<td>0.02 (0.006–0.03)</td>
</tr>
<tr>
<td>Months of NSAID minor AE</td>
<td>0.75 (0.19–1.5)</td>
<td>0.29 (0.09–0.58)</td>
<td>0.002 (0.00002–0.003)</td>
</tr>
<tr>
<td>Number of IACI major AE</td>
<td>0 (0–0)</td>
<td>0.00002 (0.000002–0.00008)</td>
<td>0.00002 (0.000002–0.00001)</td>
</tr>
<tr>
<td>Number of NSAID major AE</td>
<td>0.004 (0.0008–0.008)</td>
<td>0.002 (0.0004–0.003)</td>
<td>0.00002 (0.000001–0.00002)</td>
</tr>
</tbody>
</table>

* Values are for the base-case probabilities and model assumptions, and the values in parentheses are the most extreme values obtained in all sensitivity analyses and varied model assumptions. NSAIDs = nonsteroidal antiinflammatory drugs; IACI = intraarticular corticosteroid injection; AE = adverse effect.

### Table 4. Arthritis equivalents for the dimensions of the multi-attribute outcome as elicited by preference assessment*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Joint injection procedure</th>
<th>Oral medication for 1 month</th>
<th>Hypopigmentation</th>
<th>Stomachache for 1 month</th>
<th>Septic arthritis</th>
<th>GI bleed or kidney problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.23</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.23</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>0.03</td>
<td>1.0</td>
<td>1.0</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>0.33</td>
<td>0.07</td>
<td>0.17</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>0.47</td>
<td>0.33</td>
<td>0.03</td>
<td>0.33</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.10</td>
<td>36</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>0.23</td>
<td>0.13</td>
<td>0.03</td>
<td>1.4</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>0.23</td>
<td>0.03</td>
<td>0.03</td>
<td>0.23</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>0.03</td>
<td>0.47</td>
<td>0.03</td>
<td>0.03</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>0.23</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>60</td>
<td>1200</td>
</tr>
<tr>
<td>10</td>
<td>1.4</td>
<td>0.13</td>
<td>0.47</td>
<td>0.03</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>0.23</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>0.13</td>
<td>0.07</td>
<td>0.03</td>
<td>0.03</td>
<td>1200</td>
<td>1200</td>
</tr>
</tbody>
</table>

* Values are the number of months of active arthritis of 1 knee that were considered equivalent to the dimension under consideration. GI = gastrointestinal.
to the injection procedure. Most subjects felt that the minor adverse effects of stomachache and hypopigmentation were relatively inconsequential, although it appears that stomachache may be viewed as less desirable than hypopigmentation. Both subjects whose children had experienced minor adverse effects from NSAIDs assigned greater arthritis equivalents to NSAID minor adverse effects than to IACI minor adverse effects. By contrast, only 1 of the 4 subjects whose child had experienced an IACI minor adverse effect assigned greater arthritis equivalents to IACI minor adverse effects than to minor NSAID adverse effects. Arthritis equivalent values for the major adverse effects varied widely, from less than 1 month of arthritis up to an entire lifetime of active knee arthritis for 2 subjects.

**Optimal treatment.** The total expected arthritis equivalents for the 3 treatment strategies are shown for each of the subjects in Table 5. For 11 (92%) of 12 subjects, initial IACI was the preferred treatment strategy. For subject number 2, NSAID only was the preferred treatment strategy, due to a strong aversion for the IACI procedure. These treatment strategy preferences were unaffected by the broad sensitivity analyses of the model’s probabilities and assumptions. For all 12 subjects, the maximum possible expected arthritis equivalent value in sensitivity analyses for the preferred treatment strategy was lower than the minimum possible expected value for either of the other 2 treatment strategies (Table 5). When the NSAID trial was shortened to 1 month, 11 subjects still preferred the initial IACI treatment strategy, and this preference was insensitive to all sensitivity analyses for 10 of the 11 subjects (data not shown).

**DISCUSSION**

Combining the results of a Markov decision analysis model with probabilities based on the published literature and a novel preference assessment method, we found that 92% of subjects strongly preferred the initial IACI strategy for the treatment of knee monarthritis in their children with JIA. Preferences aside, our model predicted that, compared with the initial IACI treatment strategy, an additional 6.7 months of knee arthritis can be expected for each IACI that is averted by a 2 month trial of NSAID prior to IACI. These findings are in contrast with the recommendations of most qualitative reviews and book chapters, which recommend a trial of NSAIDs prior to IACI (2,7). However, it is estimated that 27% of pediatric rheumatologists in the US and Canada routinely utilize this initial IACI treatment strategy for knee monarthritis (8).

Ostensibly, the NSAID trial strategy is intended to decrease the number of unnecessary IACIs. However, most parent subjects in this study perceived the IACI procedure to be preferable to 0.5 months of active knee arthritis, far less than the minimum possible average of 2.2 months of arthritis that can be expected for each IACI averted by the NSAID trial strategy. Diagnostic uncertainty may represent another justification for choosing the NSAID trial strategy for treatment of knee monarthritis, but the decision tree model was based on a known diagnosis of JIA.

IACIs are obviously more invasive than NSAIDs, but in this treatment decision it appeared to be preferred by parents because it is more effective. This may reflect parents’ endorsement of the purported movement toward early, decisive therapy for JIA (79). Another study has suggested that delays in response to therapy and medication adverse effects in the treatment of JIA can negatively impact patients’ quality of life (80). Accordingly, our study should prompt a careful examination of the assumptions regarding parents’ and patients’ preferences in the treatment of pediatric rheumatic disease.

This study strongly suggests that for monarthritis of the knee in JIA, initial IACI is the optimal treatment. Given the large range of probability estimates and model assumptions for which initial IACI is the preferred treatment strategy, it may be reasonable to broadly extend this recommendation to include patients with flares of knee monarthritis with any of the subtypes of JIA, including those concurrently receiving other medications, such as methotrexate or biologic agents. The effectiveness of IACI for subtypes of arthritis other than oligoarticular/pauciarticular arthritis has been shown to be similar (25,32,34) to somewhat decreased (23). Initial IACI for monarthritis of other joints should also be strongly considered, because IACIs in other joints have comparable (81) to slightly decreased efficacy compared with IACIs in the knee (19,23). However, for some joints, IACIs may be technically more difficult and require sedation or referral to another physician (82).

An attempt was made to minimize the bias introduced by the model assumptions. NSAIDs were discontinued immediately following resolution of arthritis and the arthritis was then assumed to recur with the same probability as following successful IACI. These assumptions may not be realistic, and they bias the results toward the NSAID-containing strategies. Sedation for the IACI procedure was not included in the model or the preference assessment. The direction of the bias resulting from these

<table>
<thead>
<tr>
<th>Subject</th>
<th>NSAIDs only</th>
<th>NSAID trial</th>
<th>Initial IACI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0 (3.6–5.7)</td>
<td>2.3 (2.0–2.7)</td>
<td>0.53 (0.41–0.87)†</td>
</tr>
<tr>
<td>2</td>
<td>6.2 (3.9–8.2)†</td>
<td>14 (10–18)</td>
<td>15 (13–17)</td>
</tr>
<tr>
<td>3</td>
<td>6.8 (4.9–8.1)†</td>
<td>3.7 (3.2–4.9)</td>
<td>1.5 (1.3–2.0)†</td>
</tr>
<tr>
<td>4</td>
<td>6.8 (4.9–8.3)†</td>
<td>3.3 (2.8–4.3)</td>
<td>0.82 (0.68–1.3)†</td>
</tr>
<tr>
<td>5</td>
<td>5.1 (3.6–5.9)</td>
<td>2.1 (1.9–2.5)</td>
<td>0.29 (0.19–0.60)†</td>
</tr>
<tr>
<td>6</td>
<td>6.5 (4.3–8.5)†</td>
<td>2.9 (2.3–3.9)</td>
<td>0.53 (0.41–0.92)†</td>
</tr>
<tr>
<td>7</td>
<td>5.2 (3.7–6.1)†</td>
<td>2.4 (2.0–2.8)</td>
<td>0.53 (0.41–0.88)†</td>
</tr>
<tr>
<td>8</td>
<td>5.0 (3.6–5.7)</td>
<td>2.3 (2.0–2.7)</td>
<td>0.54 (0.42–0.88)†</td>
</tr>
<tr>
<td>9</td>
<td>9.8 (4.6–15)</td>
<td>4.7 (2.5–6.3)</td>
<td>0.55 (0.41–1.1)†</td>
</tr>
<tr>
<td>10</td>
<td>5.5 (4.0–6.4)</td>
<td>3.6 (3.0–4.5)</td>
<td>1.9 (1.7–2.5)†</td>
</tr>
<tr>
<td>11</td>
<td>5.0 (3.6–5.8)</td>
<td>2.3 (2.0–2.7)</td>
<td>0.53 (0.41–0.87)†</td>
</tr>
<tr>
<td>12</td>
<td>10 (4.7–16)†</td>
<td>4.7 (2.5–6.4)</td>
<td>0.46 (0.31–1.1)†</td>
</tr>
</tbody>
</table>

† Preferred treatment strategy.

* Values are the expected number of months of arthritis equivalents for the base-case probabilities and model assumptions, and the values in parentheses are the most extreme value from the sensitivity analyses and varied model assumptions. NSAIDs = nonsteroidal antiinflammatory drugs; IACI = intraarticular corticosteroid injection.
two assumptions is not obvious as neither the risk nor benefit of sedation was included. Medications for GI symptoms or prophylaxis were not included in the model, although their use was not restricted in the studies that produced the NSAID minor and major adverse effect probability estimates. The direction of the bias resulting from these assumptions is not obvious either. A measure of the arthritis equivalents for the need to take GI protective medications was not included, yet some benefit of GI protective medications was likely included within the model probability estimates for NSAID adverse effects. However, GI symptoms were not treated with medications in those who experienced NSAID adverse effects within the model. Not all possible treatment strategies were considered, but those included represent the approach of more than 90% of pediatric rheumatologists.

The model outcomes were assessed at 6 months for several reasons. The 6-month outcomes are presumably more reliable, as there are fewer studies available of longer-term efficacy of IACIs or, especially, for NSAIDs. Additionally, 6 months of active knee arthritis prompted all pediatric rheumatologists in a recent survey to intensify their initial treatment strategy (8). The parents’ preference for the initial IACI strategy in this study is unlikely to be affected by a longer total time horizon. The duration of arthritis dimension was the strongest determinant of this preference, due to the delay in more definitive therapy in the NSAID only and NSAID trial treatment strategies. This difference would not be offset by evaluating longer-term outcomes.

Treatment response in the model was dichotomized into resolved and not resolved. Resolution is a less subjective outcome, and disease quiescence has been proposed as the attainable and preferred objective in the current era of treatment for childhood arthritis (83). However, many studies of NSAIDs were excluded as a result. Additionally, very few studies of NSAIDs addressed outcomes for single joints, which is a problem in most clinical trial outcomes (84).

This study used a novel preference assessment technique. This hybrid of the time tradeoff and magnitude estimation techniques was chosen for several reasons. Utilities for JIA have not been established, and quantifying quality-adjusted life years for transient painful events, such as IACIs, is problematic (27). Furthermore, the aim in this study was not to establish utilities per se, but rather to assess relative preferences for the dimensions of the multi-attribute outcome. The traditional standard gamble and time tradeoff techniques have been shown to be problematic when used by parent proxies due to the difficulty in considering severe outcomes, such as death or a shortened lifespan, for their children (85,86). Parent proxies have great difficulty in reasonably considering and evaluating very rare events (86). For this reason, we asked subjects to value the certainty of the dimensions, and then we multiplied this value by the expected probability of the dimension event occurring, such that the probability of the event was not considered during the preference assessment. Individuals’ preferences for the major adverse effects varied widely (up to a 1,000-fold difference in arthritis equivalents). However, these preferences had little to no effect on individuals’ optimal treatment strategy, owing to the rareness of major adverse effects. Individuals’ preferences were analyzed separately and not combined, as the relative values of the dimensions for each individual contain the most information and combining them might have obscured this information (87).

The preference assessment had some potential limitations. The subjects were limited in number and represent a convenience sample from one pediatric rheumatology center; their preferences may not be generalizable to all parents of children with JIA. All 12 of the subjects’ children had undergone at least 1 IACI and 11 had taken chronic NSAIDs, perhaps better informing their parents’ treatment preferences. Conversely, these experiences may possibly have resulted in an outcome bias. However, this decision analysis does not aim to address the allocation of health care resources and therefore need not consider the preferences of the general population (16). Patients’ preferences were not sought due to the cognitive complexity of the preference assessment task (one-half of the children were below 8 years of age), and parents may reasonably be expected to be the decision makers in this clinical scenario.

In conclusion, using a decision analysis approach with direct assessment of preferences, initial IACI appears to be the optimal treatment strategy for monarticular juvenile arthritis of the knee in JIA. Parents’ preferences in the treatment of pediatric rheumatic diseases continue to warrant further investigation.

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AUTHOR CONTRIBUTIONS

Dr. Beukelman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Beukelman, Guevara, Albert.

Acquisition of data. Beukelman.

Analysis and interpretation of data. Beukelman, Guevara, Albert.


Statistical analysis. Beukelman.

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