Use of Concomitant Immunomodulators with Adalimumab Therapy in Pediatric Crohn’s Disease

Keith J. Benkov, George H. Russell, Charles M. Samson, Steven J. Steiner, Eileen C. King, Jesse Pratt, Samantha F. Eichner, Richard B. Colletti and the ImproveCareNow Network

ICN Community Conference, Dallas, Texas March 2019

This study was supported by AbbVie
Potential conflicts of interest

S. Eichner, employee of AbbVie
R. Colletti, consultant of AbbVie, Janssen Biotech
Introduction

- Adalimumab (ADA) is an effective agent in inducing and maintaining remission in Crohn’s disease.
- Lack of consensus on the effectiveness of Anti-TNF monotherapy vs combination therapy.
- Lack of real world clinical practice data on the use of combination therapy.
Aim

- Determine the variation in use of ADA and combination therapy in a large population of pediatric Crohn’s disease
  - Age
  - Gender
  - Type of immunomodulator
    - Thiopurine (TP)
    - Methotrexate (MTX)
  - Region of the USA
  - Changes over the last 5 years
Methods

- Retrospective cross-sectional study
- June 1, 2010 to May 31, 2015
- All consented Crohn’s disease patients
- <18 years old during the year of study
- Combination therapy defined as taking both ADA and either TP or MTX at the time of an outpatient visit
ImproveCareNow registry

- Collaborative improvement and research network
  - 87 centers, 760 pediatric gastroenterologists
  - 25,000 pediatric IBD patients
    - >80% are registered
      - >75% are consented
  - 50 to 75 data elements collected at each outpatient visit and entered into ImproveCareNow registry
Statistical analyses

- Chi-square tests to compare percentages
- Cochran Armitage Trend Test to test percentages over time and age groups
- Pairwise comparisons for comparing regions
  - Generalized linear mixed effects models with the binomial distributions
  - Logit link and Tukey-Kramer adjustment for multiple comparisons
- p-values <0.05 were considered significant
Results: Treatment with ADA

1,009 of 7,271 (14%) patients treated with ADA

- More common in
  - Males (16% vs 13%, p<0.001)
  - Older patients (p<0.001)

- Use nearly doubled over 5 years
  - From 7% to 13% (p<0.001)
Combination therapy by age

- More common in younger children
  - 63% → 43% (p=.01)
- MTX more common in younger children
  - 38% → 24% (p=0.05)
Combination therapy by gender

- Equally likely in males and females
  - 49% vs 45% (p=0.17)
- MTX > TP in males, TP > MTX in females (p<0.001)
Combination therapy over 5 years

- Increasing use each year (p<0.001)
  - 25% → 49%
  - Increasing use of MTX
  - Increasing use of TP
Variation by region of USA

- Combination therapy more common in the Midwest and West ($p<0.001$)
Limitations

- Uncertain generalizability of the results, both within and outside the USA
- Factors not examined:
  - Duration of combination therapy
  - Disease characteristics or outcomes
Discussion

- 13% of pediatric CD patients treated with ADA
- 47% treated with combination therapy
  - Considerable variation by age, gender and region
- Increasing use of combination therapy, both MTX and TP
  - Males more often treated with MTX
  - Females more often treated with TP
- Additional study is needed of the effectiveness of and indications for combination therapy
Continued Statural Growth in Older Adolescents and Young Adults with Crohn’s Disease and Ulcerative Colitis Beyond the Time of Expected Growth Plate Closure

Neera Gupta, Eileen King, Chunyan Liu, Francisco Sylvester, Dale Lee, Brendan Boyle, Anna Trauernicht, Shiran Chen, Jesse Pratt, Richard Colletti, ImproveCareNow Network
I have nothing to disclose
Statural Growth

- Statural growth is a dynamic marker of disease activity

- Statural growth impairment
  - Common in Crohn’s disease (CD)
  - Uncommon in ulcerative colitis (UC)
Bone Age (Skeletal Maturation)

- **Bone Age = 7 Years**: Small carpal epiphyses
- **Bone Age = 12 Years**: Appearance of sesamoid
- **Bone Age = 16 Years**: All epiphyses almost fused

Width of epiphyses relative to metaphyses

Wider epiphyses
Beginning of fusion
Bone Age (Skeletal Maturation)

- Bone age measurements facilitate clinically meaningful interpretation of statural growth.

- Bone age (x-ray) reflecting growth plate closure:
  - Bone age 15 years in Females
  - Bone age 17 years in Males

- Delayed bone age
  - Common in CD
  - Unknown frequency in UC (thought to be uncommon)
Bone Age (Skeletal Maturation)

- Delayed skeletal maturation results in delayed closure of growth plates and continued growth potential.

- Frequency of continued growth beyond the time of expected growth plate closure in pediatric IBD is unclear.
Study Aims

1. Determine the frequency of continued growth beyond the time of expected growth plate closure in pediatric CD vs UC.

2. Compare the total height gain beyond the time of expected growth plate closure and chronological age (CA) at achievement of final adult height in pediatric CD vs UC.

3. To describe height velocity trends in pediatric IBD compared to children participating in NHANES.
Methods

- **Study Design:** Retrospective, Observational Cohort Study

- **Source:** ICN Registry (2/14/2007 to 5/1/2017); NHANES (2007-08; 2013-14 height & height velocity data).

- **ICN Study Population:** Pediatric CD or UC Female’s ≥ CA 15 & M’s ≥ CA 17 years with height documented at ≥ 3 visits at least 6 months apart.
Methods

- **Statistical Tests:**
  - T-test
  - Chi-square test
  - Fisher's exact test
  - Wilcoxon rank sum test
  - Kaplan-Meier survival estimates
  - Log-rank tests
  - Generalized additive model
  - Descriptive statistics
Study Cohort: IBD Subtype/Sex

- N= 3007 patients
  - 2,279 (76%) Crohn’s Disease (54% Male)
  - 728 (24%) Ulcerative Colitis (44% Male)

Females ≥ CA 15 years & Males ≥ CA 17 years
# Age at Diagnosis of IBD

<table>
<thead>
<tr>
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Females ≥ CA 15 & Males ≥ CA 17 years
Frequency of Continued Statural Growth

CD M vs F
P = .014

UC M vs F
P = .86

CD vs UC
P = .0002

- CD M vs F
  - All: 81%
  - Male: 79%
  - Female: 83%
- UC M vs F
  - All: 75%
  - Male: 75%
  - Female: 74%

All - Male - Female
Frequency of Continued Statural Growth

CD M vs F
P = .014

UC M vs F
P = .86

CD vs UC
P = .0002
Frequency of Continued Statural Growth

CD M vs F
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CD vs UC
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Frequency of Continued Statural Growth

CD M vs F
P = .014

UC M vs F
P = .86

CD vs UC
P = .0002

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Continued Growth More Common in CD Females

CD M vs F  
P= .014

UC M vs F  
P= .86

CD vs UC  
P= .0002

**Continued Growth More Common in CD Females**

- **CD M vs F**: P= .014
- **UC M vs F**: P= .86
- **CD vs UC**: P= .0002
CA at Achievement of Final Adult Height &
Total Height Gain in Patients with Continued Growth

- Median CA at achievement of adult height was ~18 years in males
  and ~16 years in females.

- Overall median height gain was greater in CD males than UC males
  \( (p = 0.0004) \).

- Overall median height gain was greater in CD females than UC
  females \( (p = 0.025) \).
Final Adult Height in Males with Continued Growth

Male final adult height

- CD
- UC

Density

Height (cm)

140 150 160 170 180 190 200

0.00 0.01 0.02 0.03 0.04 0.05

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Final Adult Height Greater in UC Males than CD Males

Median (cm)

CD = 176.2
UC = 178.6

P = 0.002
Height Curves Shifted to Right in IBD Patients Continuing to Grow
# Final Adult Height Greater in Kids with Continued Growth

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<thead>
<tr>
<th>Sex</th>
<th>Dx</th>
<th>Continued to Grow</th>
<th>N</th>
<th>Final Adult Height [Median (cm)]</th>
<th>P Value</th>
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<td>Male</td>
<td>CD</td>
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<td>257</td>
<td>175.1</td>
<td>0.011</td>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>978</td>
<td>176.0</td>
<td></td>
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<tr>
<td></td>
<td>UC</td>
<td>No</td>
<td>80</td>
<td>174.7</td>
<td>0.0009</td>
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<tr>
<td></td>
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<td>Yes</td>
<td>239</td>
<td>178.8</td>
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<tr>
<td>Female</td>
<td>CD</td>
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<td>174</td>
<td>161.8</td>
<td>0.11</td>
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<td>Yes</td>
<td>870</td>
<td>162.8</td>
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<td>304</td>
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Height Velocity (CD vs NHANES)

CD-Male

- With continued growth CD Males (N=978)
- No continued growth CD Males (N=257)
- NHANES 2013-2014 Males (N=1515)

Instantaneous Growth Rate (cm/year)

Age in years
HV Greater in CD Males after Approximately CA 13 Years Suggesting Delayed BA
Limitations

- Retrospective / Missing data
- No BA data to assess height velocity BA z-scores
- Mid-parental height data are not available
- Select cohort
Summary

- Patients with IBD may continue to grow beyond the expected time of growth plate closure.

- Continued growth is more common in CD than in UC.

- Among CD patients, continued growth is more common in females than males.

- A high proportion of patients with UC exhibit continued growth, suggesting delayed BA is common in UC.

- Prospective longitudinal studies are needed.
Thank You
Evaluation of Adalimumab Effectiveness in Anti-Tumor Necrosis Factor-Naïve Pediatric Patients with Crohn’s Disease in Clinical Practice

S. Steiner, E. King, K. Park, D. Pashankar, H. Shashidhar, B. Sudel, S. Eichner, S. Chen, J. Pratt, R. Colletti, and the ImproveCareNow Network
Aims

- **Aim 1**: To measure the duration of adalimumab treatment of anti-TNF naïve pediatric Crohn’s disease patients in clinical practice

- **Aim 2**: To demonstrate the effect of adalimumab on clinical outcomes in anti-TNF naïve pediatric Crohn’s disease patients in clinical practice
Methods

- Retrospective longitudinal observational cohort study utilizing the ImproveCareNow (ICN) Registry
- All Crohn’s disease patients who received their first dose of adalimumab at <18 years of age
- No prior anti-TNF or other biologic therapy
- At least one visit following first induction dose
- Follow-up for up to 3 years following induction
- Patient assent/parent consent to use ICN Registry data for research
Results

- 174 patients identified
- Age
  - At diagnosis
    13.0 ± 3.0 yrs
  - At induction
    14.5 ± 2.5 yrs
- Sex: 57% male
- Race
  - 86% White
  - 9% Black
  - 5% other
- Ethnicity
  - 94% Non-Hispanic
  - 6% Hispanic
- Phenotype
  - B1 85%
  - B2 7%
  - B3 5%
  - B2+B3 2%
- Disease location
  - L1 19%
  - L2 17%
  - L3 58%
- Physician Global Assessment at Induction
  - Inactive 22%
  - Mild 47%
  - Moderate-Severe 31%
Duration of Follow-Up and of Adalimumab Therapy

Number of Patients

- Baseline
- 3 months
- 6 months
- 9 months
- 12 months
- 18 months
- 24 months
- 30 months
- 36 months

- On adalimumab
- Off adalimumab
Steroid Free Remission of Patients Still Taking Adalimumab
### Induction Dosing

**Sum of the Two Induction Doses**

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<thead>
<tr>
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<th>&lt; 40 kg (n=35)</th>
<th>&gt;40 kg (n=139)</th>
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<tbody>
<tr>
<td>120 mg</td>
<td>18 (53%)</td>
<td>7 (5%)</td>
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<tr>
<td>240 mg</td>
<td>11 (32%)</td>
<td>122 (88%)</td>
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<tr>
<td>Other</td>
<td>6 (15%)</td>
<td>10 (7%)</td>
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## Maintenance Dosing at 12 months

$$mg \text{ Adalimumab/2 weeks}$$

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<tr>
<td>20 mg</td>
<td>4 (17%)</td>
<td>0</td>
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<td>40 mg</td>
<td>14 (61%)</td>
<td>88 (87%)</td>
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<td>80 mg</td>
<td>4 (17%)</td>
<td>12 (12%)</td>
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<td>Other</td>
<td>1 (4%)</td>
<td>1 (1%)</td>
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<td>4</td>
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Concomitant Therapy

- No difference in Steroid Free Remission Rate by PGA at 6 months (n=160) or 12 months (n=142) post-induction
  - Thiopurine
  - Methotrexate
  - Either thiopurine or methotrexate
Reasons for Discontinuation of Adalimumab

- Primary non-responder: 11 (6%)*
- Secondary loss of response: 6 (3%)
- Allergic reaction: 1
- Patient choice: 1
- Insurance: 1

* Of total patients treated with adalimumab
Conclusions

- Adalimumab is highly effective in anti-TNF naïve pediatric Crohn’s disease in clinical practice
  - 94-97% of patients remained on therapy for 6-24 months follow-up
  - Few primary non-responders (6%)
  - Steroid-free remission rates of 75-95% over 6 to 24 months follow-up
- Patients <40kg often required increased maintenance dosing
- No significant change in remission rates with concomitant immunomodulator therapy
Evaluation of Adalimumab Effectiveness in Paediatric Patients with Ulcerative Colitis in Clinical Practice

S. Steiner, C. Liu, E. King, E. Israel, B. Pasternak, M. Schaefer, S. Chen, J. Pratt, A. Lazar, M. Bereswill, A. Robinson, R. Colletti, and the ImproveCareNow Network
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  - At induction
    14.8 ± 2.7 yrs
- Sex: 58% female
- Race
  - 79% White
  - 14% Black
  - 8% other
- Ethnicity
  - 94% Non-Hispanic
  - 6% Hispanic
- Disease location
  - Pancolitis 67%
- Physician Global Assessment at Induction
  - 25% Inactive
  - 39% Mild
  - 33% Moderate
  - 3% Severe
- PUCAI at Induction
  - 66% <35
  - 34% ≥35
Duration of Follow-Up and of Adalimumab Therapy

Number of Patients

<table>
<thead>
<tr>
<th>Time Period</th>
<th>On adalimumab</th>
<th>Off adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Steroid Free Remission of Patients Still Taking Adalimumab

Baseline | 3... | 6... | 9... | 12... | 18... | 24... | 30... | 36...

Percentage

PUCAI | PGA
## Induction Dosing

### Sum of the Two Induction Doses

<table>
<thead>
<tr>
<th></th>
<th>&lt; 40 kg (n=22)</th>
<th>&gt;40 kg (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 mg</td>
<td>9 (69%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>240 mg</td>
<td>1 (8%)</td>
<td>67 (84%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (23%)</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Missing</td>
<td>9</td>
<td>31</td>
</tr>
</tbody>
</table>
### Maintenance Dosing at 12 months

**mg Adalimumab/ 2 weeks**

<table>
<thead>
<tr>
<th>Dose</th>
<th>&lt; 40 kg (n=14)</th>
<th>&gt;40 kg (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40 mg</td>
<td>7 (78%)</td>
<td>29 (63%)</td>
</tr>
<tr>
<td>80 mg</td>
<td>2 (22%)</td>
<td>15 (33%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>
Concomitant Therapy

No difference in Steroid Free Remission Rate by PGA at 6 or 12 months

- Thiopurine, Methotrexate, or Either Thiopurine/Methotrexate

<table>
<thead>
<tr>
<th>Therapy</th>
<th>6 months (n=77)</th>
<th>12 months (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopurine</td>
<td>21%</td>
<td>16%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>17%</td>
<td>16%</td>
</tr>
<tr>
<td>Thiopurine or Methotrexate</td>
<td>38%</td>
<td>31%</td>
</tr>
</tbody>
</table>
Colectomy Rate
Safety

- 14 hospitalizations in 8 patients (13 UC related)
- 5 serious infections in 5 patients
  - CMV
  - Cryptosporidium
Conclusions

- ~80% of patients who started on adalimumab remained on therapy from 6 months through 3 years
- ~70% of patients are in steroid free clinical remission by 12- 24 months
- Colectomy free estimates are 86% at 12 months and 80% at 24 months
- No significant change in remission rates with concomitant immunomodulator therapy
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