Diagnosis and treatment of inflammatory bowel disease in children
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Part 2
Pharmacokinetic studies
Pharmacokinetics of budesonide controlled ileal release capsules in children and adults with active Crohn's disease

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Submitted for publication
Abstract

Background
Systemic glucocorticosteroid therapy is effective in Crohn's disease (CD) but the therapy is associated with side effects. Budesonide has high topical anti-inflammatory activity but considerably lower systemic activity than other oral glucocorticosteroids.

Aim
To evaluate the systemic exposure of budesonide (CIR capsules) in children and adults with active CD, and to assess suppression of plasma cortisol.

Methods
In an open label study, patients (8 children, 6 adults) with active CD received 9 mg budesonide (Entocort® capsules) orally once daily for seven days. Plasma concentrations of budesonide were determined on the seventh day of oral treatment, and pharmacokinetic parameters were calculated. For reference, 0.5 mg budesonide was given intravenously on a separate occasion. Plasma cortisol levels on day 7 were compared with pre-treatment baseline.

Results
Systemic exposure of budesonide (AUC_{0-24h}) after one week's oral administration was 41 (21) nmol/L x h, mean (± SD), in children and 35 (20) nmol/L x h in adults. The estimated systemic availability in children was 9 (5) %, and in adults 11 (7) %. Mean plasma cortisol (AUC_{0-24h}) decreased by 64 (18) % in children and by 50 (27) % in adults.

Conclusions
Systemic exposure, systemic availability and cortisol suppression after oral administration of 9 mg budesonide CIR were similar in children and adults with active Crohn's disease. Budesonide was well tolerated and no clinically important safety related findings were identified.
Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disorder of unknown aetiology that may affect any part of the gastrointestinal tract. In both children and adults, the most common sites for the inflammation are the distal ileum and/or the ascending colon\(^1\). The first symptoms of CD can develop at an early age; the incidence of CD in patients 15 years of age or less was 1.2-1.3 per 100,000 in Sweden\(^2\) representing about 15-20% of the total incidence. Early manifestations of CD in these young patients include impaired growth and delayed puberty\(^3\). Systemic glucocorticosteroids are still the primary treatment for exacerbation of inflammation, but these drugs are associated with clinically important acute side effects such as acne, and Cushingoid features. In the pediatric age group, long-term corticosteroid treatment may result in growth failure and retardation of puberty.

Budesonide is a potent glucocorticosteroid that has high anti-inflammatory activity, but considerably lower systemic activity than conventional steroids\(^4\).

Budesonide Controlled Ileal Release (CIR) capsules are approved for once daily treatment of active mild to moderate Crohn's disease in adults. These capsules release budesonide to the whole intestinal tract, but on average 60-80% of the oral dose is absorbed in the ileum and along the colon in both healthy volunteers and CD patients\(^5,6\). In clinical studies in adults, budesonide CIR capsules 9 mg once daily were more effective than placebo\(^7\), and similar efficacy as prednisolone, 40 mg, in the treatment of adults with active CD affecting the ileum and/or ascending colon, while having fewer side effects\(^8,9\).

Budesonide has a longstanding record as a safe and efficacious treatment of pediatric asthma and rhinitis\(^10,11\). In pediatric patients, both budesonide enema for ulcerative colitis and budesonide capsules for Crohn's disease induced clinical remission and had a significantly less suppression of plasma cortisol than the corresponding prednisolone treatment\(^12,13\). In the face of the acute cosmetic side effects leading to non-compliance, and the effects on growth as a long-term concern, oral budesonide seems to be a safe alternative for
conventional steroid treatment of children with active Crohn’s disease. A pharmacokinetic study of oral budesonide has never been performed in children with Crohn’s disease. Pediatric protocols traditionally involves weight- or age-based reductions in dose. Efficacy at these doses have generally not been sufficiently proven and pediatric patients therefore stands a greater risk of being treated with inadequate doses.

The primary aim of the present study was to evaluate the systemic exposure of budesonide in children and adults with CD after administration of budesonide CIR capsules, 9 mg once daily. A secondary aim was to compare the suppression of plasma cortisol in the two study populations after 1 week of budesonide intake.

**Materials and Methods**

**Patients**
Inclusion criteria were age, 6 to 14 years of age for children-adolescents and 18 to 70 years for adults, body weight > 20 kg, a diagnosis of CD verified prior to inclusion by colonoscopy including histology and/or radiology. Active CD was defined as a pediatric Crohn’s Disease Activity Index (PCDAI\(^{14}\) > 25 or Crohn’s Disease Activity Index (CDAI\(^{15}\) > 150 (children) and CDAI > 200 (adults) and the disease had to be at least in the ileum and/or ascending colon, with an intact ileocecal valve. Patients were excluded if they had a history of gastric surgery, ileal resection of more than 50 cm (children) and 100 cm (adults), ileostomy, were pregnant, likely to become pregnant or were breast-feeding.

A constant dose of 5-ASA products and azathioprine was allowed during the study, but the use of any other immunosuppressive agent was prohibited within 3 months of inclusion, as were any corticosteroids, imidazoles, triazoles, rifampicin and/or erythromycin and oral contraceptives within 2 weeks of
inclusion. Treatment with cholestyramine and loperamide was not allowed within a week of inclusion.

**Study design**

The study protocol consisted of five clinic visits; inclusion at visit 1, baseline plasma cortisol and calculation of disease activity index at visit 2 and at visit 3 budesonide was given as a single intravenous infusion (to four children and to six adults). After six days of oral administration of budesonide the seventh dose was taken at the clinic (visit 4) and visit 5 was for follow-up. There were at least seven days between visits 3 and first dose in visit 4.

**Intravenous administration**

The budesonide solution for intravenous infusion (25 µg/ml) was infused over 10 minutes (2 ml/min) into an arm vein via an indwelling catheter (Venflon®) at about 8.00 a.m. The estimated dose was 0.5 mg, whereas the exact dose given was determined by weighing the syringe before and after administration. Blood samples were collected before and 10, 20, 40, 60, 90 min and 2, 4, 6 and 8 hours after start of infusion. Blood samples were drawn from an indwelling catheter inserted into an arm vein (the contra-lateral arm to the infusion arm) or taken by venepuncture. When Venflon was used, the first millilitre was discarded. Na-heparinized (Venoject®) tubes, 5 ml (children) and 7 ml (adults), were used for sample collection at each time point. The tubes were immediately centrifuged, and the plasma frozen and stored at -70°C until analysis.

**Oral administration**

The patients took budesonide CIR capsules 3 x 3 mg in the morning (at 8.00 a.m. together with 200 ml water) for seven days. The seventh dose was given at the clinic. A standardised breakfast was served immediately after dose
intake. Blood samples were taken just before and 0.5, 1, 2, 3, 4, 6, 9, 12 and 24 hours after dose intake.

The determination of budesonide, done at the Department of Development Drug Metabolism & Bioanalysis at AstraZeneca R&D Lund, was based on liquid chromatography and tandem mass spectrometry. The lower limit of quantification (LOQ) was 0.025 pmol when 1 millilitre was analysed. The between-run coefficient of variation in quality control samples run in parallel with the study samples was 7-15% at 0.025 pmol, 10-14% at 0.050 pmol, and less than 6% at higher levels of budesonide.

Food
The patients had to fast (food and beverage) for at least 10 hours before they arrived at the clinic in the morning for blood sampling. The patients were instructed to drink 200 ml water and eat a standardized breakfast (two slices of white bread with cheese and 300 ml coffee, tea, juice or water). The lunch was chosen by the patient and was of the same composition for all visits at the clinic, and served at noon (four hours after dose administration). The patients were allowed to eat and drink freely two hours after lunch. Grapefruit juice was not allowed for six hours after dose intake, nor was alcoholic beverages allowed 24 hours prior to or during any study-related activity.

Plasma cortisol
Blood samples for plasma cortisol were taken at two visits, at baseline (no treatment) and at the seventh oral dose at 0, 3, 6, 9, 12, 15, 18, 21 and 24 h after 8 a.m. Blood samples were drawn from an indwelling catheter inserted into an arm vein or taken by venepuncture. Na-heparinized (Venoject) 2 ml tubes, were used for sample collection at each time point but only one millilitre was collected. The tubes were then immediately centrifuged (1500 x g) for 10 minutes. The plasma was removed, transferred to a polystyrene tube and stored frozen at -20°C until analysis. The cortisol assay was based on gas chromatography/mass spectrometry, negative ion chemical ionization16. The
limit of quantification was 20 nmol/L, and the coefficient of variation at 57, 721 and 1200 nmol/L were 5.4%, 7.1% and 5.9%, respectively.

**Pharmacokinetic assessments**
The terminal elimination rate constant ($k_{el}$) was estimated from the concentration-time curve using linear regression of $\ln C(t)$ vs. $t$. When computing pharmacokinetic parameters the elimination rate obtained from the intravenous administration was used. All integrals over regions of observation are computed using the trapezoidal rule. Extrapolation is done using a monoexponential extrapolation based on the terminal elimination rate.

*Calculation of Nonparametric PK parameters*
From the intravenous administration the following parameters are calculated;

Area under the plasma concentration-time curve (AUC) = $\int_0^\infty C(t)dt$,

Area under the first moment-time curve (AUMC) = $\int_0^\infty tC(t)dt$,

Half-life ($T_{1/2}$) = $\ln 2 / k_{el}$,

Mean residence time (MRT) = AUMC / AUC,

Clearance (CL) = Dose /AUC,

Distribution volume ($V_{dist}$) = CL /$k_{el}$

Volume at steady state ($V_{ss}$) = CL x MRT.

For the oral, multiple dosing regimes, steady state is assumed to be reached and the following parameters computed, in addition to obvious ones, $C_{max}$ and $T_{max}$:

Systemic availability (F) = $\frac{AUC / Dose}{AUC_{iv} / Dose_{iv}}$,

Mean absorption time (MAT) = $MRT_{oral} - MRT_{i.v.}$.

In four children lacking i.v. data, the systemic availability was estimated by substituting their oral dose and AUC with the average i.v. dose and average
AUC_{i.v.} in the children who did have i.v. data. Similarly, the i.v. dose and AUC for the adult patient who had a conspicuous i.v. curve was replaced by the average dose and average AUC_{i.v.} in the other adults. No other PK i.v. parameters were estimated for this subject.

**Pharmacodynamic assessments**
Plasma cortisol concentrations below the limit of quantification (LOQ) were estimated with LOQ/2. The 24-hour plasma cortisol concentration was calculated as AUC by the trapezoidal formula.

**Statistics**
The pharmacokinetic parameters and plasma cortisol were described with 95% confidence limits (based on the normal distribution) for the ratio or difference between children and adults. A multiplicative model (data were log-transformed before analysis and the results given as ratios) was used for analysis of AUC, C_{max}, F, CL, V, T_{1/2}, and an additive model for T_{max}, MRT and MAT (results given as differences). Groups were compared using a t-test.

**Safety**
Adverse events were collected by means of a standard question, and spontaneously reported and/or observed AEs and the response was recorded with information about seriousness, date of onset and recovery, duration, maximum intensity, action taken and outcome. The patients were asked to assess the intensity of the reported adverse events according to the following scale: Mild, Moderate or Severe.

All new or aggravated findings at physical examination, laboratory examinations and vital signs compared with baseline had to be identified and commented. These were considered adverse events.
Ethical review
The protocol was approved by local and national Ethics Committees in Sweden and in Canada. Written and verbal informed consent was obtained from the adult patients, children and/or from the children's parents/legal guardians prior to any study-specific procedure.

Results
All patients were Caucasian. Two adult patients were current smokers, and one was a former smoker. All children were prepubertal. Demographics of the patients are shown in Table 1.

Table 1. Demographics of treatment groups, mean (SD) or *individual data

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>5/3</td>
<td>5/1</td>
</tr>
<tr>
<td>Age at inclusion (years)</td>
<td>12.4 (1.8)</td>
<td>33.2 (12.6)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>39.8 (6.1)</td>
<td>64.3 (13.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>153 (11)</td>
<td>170 (10)</td>
</tr>
<tr>
<td>CDAI</td>
<td>237 (112)</td>
<td>320 (54)</td>
</tr>
<tr>
<td>PCDAI</td>
<td>36.6 (10.5)</td>
<td>-</td>
</tr>
<tr>
<td>Localisation of disease*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prox small intestine and rectum</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ileum</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>ileum + colon</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Intravenous administration

The mean (SD) intravenous dose was 1142 (10) nmol in children and 1163 (24) nmol in adults. The individual plasma concentrations are shown in Figure 1 for both the children and the adult patients. In one adult patient, plasma concentrations of budesonide deviated extremely compared to the other patients: the concentration just prior to dose (12 nmol/L), suggested off-study budesonide administration or sample contamination. This patient was excluded from the descriptive statistics and calculation of mean concentrations after i.v. infusion (see Table 2). Because of the elaborate study protocol, only four children agreed to participate in the intravenous part of the study.

**Figure 1.** Individual plasma budesonide concentrations after i.v. administration in children (dotted lines) and in adults (solid lines)
The mean systemic exposure, AUC_{i.v.}, for budesonide after intravenous administration was 24 nmol/L x h in children and 19 nmol/L x h in adults (Table 2). Clearance, CL, was on average slightly higher in adults (1.02 L/min) as compared with children (0.81 L/min). After weight normalization, clearance was higher in children (20.5 ml/min/kg) than in adults (15.9 ml/min/kg). The volume of distribution, V_{ss}, was higher in adults than in children, 148 L and 84 L, respectively (Table 2). The elimination half-life, T_{1/2}, was on average 1.9 h in pediatric and 2.7 h in adult patients.

Table 2. Pharmacokinetic parameters after i.v. administration of budesonide, mean (SD) and ratio or difference (lower and upper 95% confidence limits)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Children (n = 4)</th>
<th>Adults (n = 6)</th>
<th>Ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{i,v} (nmol/L x h)</td>
<td>24.5 (5.0)</td>
<td>19.3 (2.3)</td>
<td>1.2 (0.97 to 1.6)</td>
</tr>
<tr>
<td>CL (L/min)</td>
<td>0.81 (0.21)</td>
<td>1.02 (0.15)*</td>
<td>0.8 (0.6 to 1.06)</td>
</tr>
<tr>
<td>CL (ml/min/kg)</td>
<td>20.5 (3.7)</td>
<td>15.9 (4.8)*</td>
<td>1.3 (0.9 to 2.0)</td>
</tr>
<tr>
<td>V_{ss} (L)</td>
<td>84 (13)</td>
<td>148 (28)*</td>
<td>0.6 (0.4 to 0.8) (P=0.0022)</td>
</tr>
<tr>
<td>V_{ss} (L/kg)</td>
<td>2.2 (0.4)</td>
<td>2.3 (0.5)*</td>
<td>0.96 (0.7 to 1.4)</td>
</tr>
<tr>
<td>V_{det} (L)</td>
<td>129 (19)</td>
<td>229 (53)*</td>
<td>0.6 (0.4 to 0.8) (P=0.0039)</td>
</tr>
<tr>
<td>T_{1/2} (h)</td>
<td>1.9 (0.2)</td>
<td>2.7 (0.9)*</td>
<td>0.7 (0.5 to 1.07)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>1.8 (0.3)</td>
<td>2.5 (0.7)*</td>
<td>-0.7** (-1.6 to 0.2)</td>
</tr>
</tbody>
</table>

*n = 5. **difference, not ratio

Oral administration

The individual plasma concentrations after oral administration are shown in Figure 2. After one week of once-daily oral administration of 9 mg budesonide, systemic exposure, AUC_{oral}, was on average 41 nmol/L x h in children and 35 nmol/L x h in adults (Table 3). The mean maximal concentration after oral
administration, $C_{\text{max}}$, was 6.0 nmol/L in children and 4.0 nmol/L in adults (Table 3). Systemic availability, $F$, was on average 9% (range 3 to 17%) in children and 11% (range 3 to 21%) in adults. Time to maximal plasma concentration, $T_{\text{max}}$, after oral administration was on average 4.7 h in children and 4.3 h in adults. The mean time budesonide reside in the body, MRT, was also similar in children and in adults (Table 3). The mean absorption time (MAT) did not differ significantly between the four children and the five adults. As previously described, $F$ for the four children not receiving i.v. budesonide was based on mean $\text{AUC}_{\text{i.v.}}$ from the four children with i.v. data. When sample means ($\text{AUC}_{\text{oral}}, C_{\text{max}}, T_{\text{max}}, F, \text{MRT}_{\text{oral}}, \text{MAT}$) were statistically compared between the two study populations, there were no significant differences.

**Figure 2.** Individual plasma budesonide concentrations after oral administration in children (dotted lines) and in adults (solid lines)
Table 3. Pharmacokinetic parameters after oral administration of budesonide, values presented as mean (SD) and ratio or difference (lower and upper 95% confidence limits)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Children (n = 8)</th>
<th>Adults (n = 6)</th>
<th>Ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;oral&lt;/sub&gt; (nmol/L x h)</td>
<td>41.3 (21.2)</td>
<td>35.0 (19.8)</td>
<td>1.2 (0.6 to 2.6)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (nmol/L)</td>
<td>6.0 (3.4)</td>
<td>4.0 (2.1)</td>
<td>1.4 (0.6 to 3.6)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>4.7 (2.6)</td>
<td>4.3 (1.5)</td>
<td>0.4** (-2.2 to 3.0)</td>
</tr>
<tr>
<td>F (%)</td>
<td>9.2 (4.6)</td>
<td>10.6 (7.0)</td>
<td>0.9 (0.4 to 2.1)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>9.1 (3.9)</td>
<td>8.8 (1.8)</td>
<td>0.4** (-3.4 to 4.2)</td>
</tr>
<tr>
<td>MAT (h)</td>
<td>8.1 (4.6)*</td>
<td>6.3 (1.8)</td>
<td>1.7** (-3.5 to 6.9)</td>
</tr>
</tbody>
</table>

* n = 4, † n = 5, ** difference, not ratio

Plasma cortisol results
During the 24 hours following the seventh oral dose of budesonide, the average AUC for plasma cortisol showed a decrease of 64% (range 37-92%) in the children and of 50% (range 18-89%) in the adults compared to baseline (difference not statistically significant). The 95% confidence interval for the ratio between children and adults was 1.42 (0.84 to 2.41). The maximum plasma cortisol concentration was generally observed between 2 a.m. and 8 a.m. The morning (8.00 a.m.) values of the plasma cortisol suppression were on average 27% (range 0-68%) in children and 25% (range 0-94%) in adults.

Safety
No clinical response was expected due to the short treatment period. The few reported adverse events were mainly related to the underlying disease or isolated symptoms. No clinically important safety related findings were identified.
Pharmacokinetics 2.1

Discussion

The main pharmacokinetic parameter for evaluation of differences in systemic exposure in children and adults, AUC\textsubscript{oral}, was somewhat higher in children (41 nmol/L x h) as compared to adults (35 nmol/L x h) following 9 mg budesonide CIR for a week. Peak plasma concentration, C\textsubscript{max}, was on average higher in children than in adults indicating a higher peak exposure in children after the oral budesonide dose. The variability in the measured parameters was large, due to the small number of patients studied but similar in the two groups. The systemic availability, F, was on average 9% in children and 11% in adults, similar to what has been previously reported in fasting patients with active CD\textsuperscript{17}. Statistical analyses did not reveal any differences between adults and children in either rate of absorption, T\textsubscript{max} and MAT, or extent of absorption expressed as oral AUC\textsubscript{0-24h}.

Budesonide is a substrate for cytochrome P450 (CYP) 3A4, a drug-metabolizing enzyme which appears to have the same activity in children 9 to 14 years old as in adults\textsuperscript{18}. The mean clearance was estimated to 0.81 L/min in children and 1.02 L/min in adults. If clearance is calculated on a per kilogram basis, the children had about 30% higher clearance than adults, and if calculated on a body surface area basis, the CL was 5-10% higher in children. This confirms previous findings\textsuperscript{19,20} and supports the concept of a higher liver blood flow per kilogram body weight in children. The volume of distribution was significantly lower in children (84 L) than in adult patients (148 L). As clearance was similar for the two groups but V\textsubscript{ss} differed, the resulting half-life (T\textsubscript{1/2}) was shorter in the children than in the adults (1.9 vs. 2.7 hours, respectively). The weight corrected V\textsubscript{ss} was, however, similar for children (2.2 L/kg) and adults (2.3 L/kg).

One may speculate as to whether chronic intestinal inflammation will increase systemic exposure of budesonide, for instance by an impaired intestinal barrier function and/or reduced presystemic elimination. The present data do not
suggest that this is the case, since there was no correlation between disease activity indexes (PCDAI or CDAI) and AUC<sub>oral</sub> or systemic availability. Moreover, the systemic availability of oral budesonide (ranging from 9% to 12%) previously reported in healthy volunteers<sup>5</sup> is similar to the data in the present study. Corresponding numbers in healthy pediatric subjects are not available.

Plasma cortisol (measured as AUC<sub>0-24h</sub>) decreased after one week's treatment with budesonide CIR capsules. The decrease in mean AUC<sub>0-24h</sub> from baseline to end of treatment was on average 64% in children and 50% in adults. This is similar to what has previously been found for budesonide in healthy adults, 51% (range 23-67%), and significantly less than for equi-effective doses of prednisolone<sup>21</sup>. Also the mean suppression of plasma cortisol at 8.00 a.m. (about 25% compared to baseline) conforms to results from previous studies in patients where the same dose was given<sup>7,9</sup>. The two patients who had the highest budesonide AUC<sub>oral</sub> also had the largest plasma cortisol suppression.

The budesonide CIR capsule formulation comprise granules with a pH-dependant enteric coating covering a budesonide matrix which releases drug in a time-dependant fashion in the ileum throughout the colon<sup>22</sup>. As pH and intestinal transit is similar in children as in adults<sup>23,24</sup>, the budesonide CIR capsule formulation should be well adapted for local delivery also in children.

The present pharmacokinetic and pharmacodynamic data suggests that the systemic exposure and systemic effects, measured as cortisol suppression, are similar in children as in adults. Recent data in asthmatic children, aged 2 to 6 years, also suggest that systemic exposure is independent of age<sup>25</sup>. Hence, the benefits associated with budesonide treatment should always be weighed against the risks in any child needing steroids for treatment of Crohn's disease, routine weight-related dose reduction schemes may not be a necessity in this patient group. Based on these findings, a dose of 9 mg/day of budesonide was
successfully used in the pediatric multicenter trial of budesonide versus prednisolone in active Crohn’s disease\textsuperscript{13}.

In conclusion, budesonide given intravenously and as CIR capsules was well tolerated and no clinically important safety related findings were identified in this study. The systemic exposure, systemic availability and cortisol suppression after oral administration of 9 mg budesonide CIR were similar in pediatric (>30 kg) and adult patients with active Crohn’s disease.
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   Gastroenterology 2001;120 (Suppl 1):A749, 4024. Abstract


Infliximab therapy in the treatment of pediatric Crohn's Disease

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Submitted for publication
Abstract

Objective
To assess the efficacy and safety of a single infusion of infliximab in the treatment of pediatric Crohn's disease (CD).

Methods
Twenty-one pediatric CD patients were randomized to receive a single infusion of infliximab 1 mg/kg (n=6), 5 mg/kg (n=7), or 10 mg/kg (n=8) over at least 2 hrs at Week 0 in this multicenter open-label trial. Efficacy assessments, including the Pediatric Crohn's Disease Activity Index (PCDAI), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) determinations, were made at screening and at Weeks 1, 2, 4, 8, and 12. Adverse events were assessed throughout study participation.

Results
Improvements in the PCDAI, ESR, and CRP were observed with all infliximab doses beginning at Week 1. On average, all treated patients experienced approximately 53% improvement in the PCDAI by Week 2. By Week 12, the PCDAI remained approximately 30% improved from baseline. During the study, all 21 (100%) patients achieved a clinical response and 10 patients (47.6%) achieved clinical remission. There were no infusion reactions in any of the treatment arms.

Conclusions
The results of this trial suggest that infliximab may be safe and effective as short-term therapy of medically refractory moderate to severe CD in a pediatric population.
Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disorder characterized by transmural, granulomatous inflammation, involving any part of the gastrointestinal tract in a discontinuous manner. The peak incidence of CD occurs during the adolescent and young adult years. Conventional therapies such as corticosteroids and immunomodulators are the mainstay of management protocols for children with CD. Most children with CD will experience ongoing disease activity over the course of their lives complicated by the need for prolonged medical and surgical management. Side effects of current management include impaired growth, osteoporosis, the risk of hepatitis, and bone marrow suppression. Approximately 40% of patients require surgical resection. New approaches to the management of pediatric CD are currently needed.

Tumor necrosis factor-alpha (TNFα) is a targeted proinflammatory cytokine that is very proximal in the cytokine cascade and mediates the production of other inflammatory cytokines. TNFα has been demonstrated to play an important role in CD and other granulomatous diseases. A chimeric anti-TNFα monoclonal antibody, infliximab (REMICADE®) is a potent anti-inflammatory agent that binds to TNFα with high affinity and specificity, thereby neutralizing its biological activity. The use of infliximab for short-term therapy (single infusion of 5 mg/kg) has proved beneficial for adults with moderately to severely active CD for the reduction of the signs and symptoms among patients who have an inadequate response to conventional therapy. In addition, infliximab is indicated for patients with fistulizing disease, in whom an initial 5 mg/kg dose is followed with additional 5 mg/kg doses at 2 and 6 weeks after the initial infusion.

The success of infliximab therapy in adult CD patients prompted evaluation of this agent in children with refractory disease. In an evaluation of 15 children who received a single 5 mg/kg infusion of infliximab, 94% (14/15) of the
patients showed improvement in their CD, with a significant decrease of both the Pediatric Crohn's Disease Index (PCDAI) and daily steroid use by 4 weeks following infusion\(^9\). A separate group of 19 children and adolescents with active intestinal CD who had received one to three infliximab infusions (5 mg/kg) over a 12-week period were the subject of a retrospective chart review. Significant decreases in the mean PCDAI and mean prednisone dosages were observed\(^9\). No limiting toxicities were observed in either of the patient populations\(^9,10\).

The current trial was undertaken to assess the efficacy, safety, and pharmacokinetics of three doses of infliximab in pediatric patients with active CD.

**Patients and Methods**

*Eligibility.* Patients between the ages of 8 and 17 years with a history of CD for at least the previous 6 months were eligible for study participation; a baseline PCDAI $\geq$30, indicating moderate to severe disease, was required. Patients were required to present with active disease despite treatment with one of the following: 1) oral corticosteroids (maximum of 40 mg/day for at least the previous 2 months and a stable dose in excess of 10 mg/day for at least the previous 3 weeks), 2) 6-mercaptopurine (at least 0.8 mg/kg) or azathioprine (at least 1.5 mg/kg), 3) methotrexate (at least 4 months use and at a stable dose of at least 10 mg/m\(^2\)/week for at least the previous 6 weeks), 4) cyclosporine (at least 2 weeks of 4 mg/kg/day or higher), or 5) tacrolimus (at least 2 weeks of 0.15 to 0.2 mg/kg/day). If patients were not using these therapies, the stop date must have been at least 4 weeks prior to screening. Patients were excluded from participation if they had received treatment with cyclosporine or total parenteral nutrition within 4 weeks of screening. The presence of draining enterocutaneous fistulas was allowed.
Patients or legal guardians provided written informed consent for this study prior to any protocol-specific procedure. The study was conducted in accordance with regulations governing clinical trials including the Code of Federal (US) Regulations and the Declaration of Helsinki.

**Study and concomitant medications.** Patients were treated with infliximab (REMICADE®, Centocor, Inc, Malvern, PA) 1, 5, or 10 mg/kg at Week 0. Patients and investigators were blinded to the assignment of infliximab dose. The study medication was prepared based on the patient’s weight. Infliximab was administered via a separate line using the administration supplies provided. The infusion was delivered over at least 2 hours. All medications other than infliximab were continued without change. At Week 4, the dosage of corticosteroids was decreased by 5 mg/week if the initial dose was >20 mg/day, or by 2.5 mg/week if the initial dosage was <20 mg/day.

**Study procedures and outcomes.** Patients were screened to establish baseline PCDAI and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentrations. The PCDAI includes 11 variables related to the disease, including weight, height, abdominal mass, perirectal disease, extraintestinal manifestation, hematocrit, ESR, albumin, abdominal pain, number of liquid stools, and general well-being. Scores range from 0 to 100, with 10 and under indicating inactive disease, 11 to 30 mild disease, and >30 considered moderate to severe disease. Body weight and vital signs were measured prior to infliximab infusion. Follow-up PCDAI assessments and ESR and CRP determinations were made at Weeks 1, 2, 4, 8, and 12. Patients were requested to have an endoscopy performed for evaluation of mucosal inflammation at baseline and Week 4. These endoscopies were evaluated and the endoscopic lesion severity score was derived using a 10-cm visual analog scale (0=healed, 10=very severe disease). Blood samples for determination of serum infliximab concentrations were collected prior to infusion, 1 hour following infusion completion, and at each subsequent study visit. Samples for determination of antibodies to infliximab (ATI) were collected at Weeks 0, 4, 8,
12, and 20; those for determination of antibodies to double-stranded (ds) DNA were obtained at Weeks 0, 8, and 20. Adverse events rated by the investigator as possibly, probably, or definitely related to the study agent were classified as reasonably-related adverse events.

**Randomization procedure and statistical analysis.** Patients were assigned to infliximab dose stratified by age (<13, 13-17). The prespecified primary efficacy parameters were improvements from baseline in the PCDAI score and in the CRP and ESR concentrations. Secondary measures of efficacy were clinical response, defined as a ≥10-point improvement in the PCDAI, and clinical remission, defined as a PCDAI <10. Serum concentrations of infliximab were summarized by dose group over time. Derived pharmacokinetic parameters also were determined and compared to pharmacokinetic results obtained following a single infusion of 1, 5, or 10 mg/kg infliximab in adult CD patients studied in a separate infliximab clinical trial.
Table 1. Baseline patient and disease characteristics of 21 pediatric CD patients.

<table>
<thead>
<tr>
<th></th>
<th>Infliximab dose</th>
<th>All Patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/kg (n=6)</td>
<td>5 mg/kg (n=7)</td>
</tr>
<tr>
<td>Median age (yrs)</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Gender (number, %)</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>3 (50.0)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Median weight (kg)</td>
<td>47.1</td>
<td>45.1</td>
</tr>
<tr>
<td>Mean disease duration (yrs)</td>
<td>2.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Involved intestinal areas (number, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited to ileum</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Limited to colon</td>
<td>1 (16.7)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Ileum and colon</td>
<td>5 (83.3)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Gastroduodenum</td>
<td>4 (66.7)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Number (%) of patients with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous segmental resection</td>
<td>0</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>Enterocutaneous fistulas</td>
<td>2 (33.3)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Median baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCDAI (0-100)</td>
<td>56</td>
<td>45</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>52</td>
<td>33</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>4.2</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Results

Patient disposition and baseline characteristics. Twenty-one patients were enrolled and treated with infliximab. Eighteen patients were evaluated for efficacy through Week 12. Baseline patient and disease characteristics are summarized in Table 1. The 21 study participants ranged in age from 11 to 17 years (median of 15 years). Overall, both the ileum and colon were affected in the majority of patients. The baseline PCDAI scores ranged from 30 to 73 (median of 43); all patients had either moderate (43%, 9/21 patients) or severe (57%, 12/21 patients) disease as determined by the investigator.

Concomitant medications: Concomitant medication use at baseline is summarized in Table 2. The majority of patients were receiving concomitant corticosteroids (91%, 19/21 patients) and oral aminosalicylates (81%, 17/21 patients) at screening.

<table>
<thead>
<tr>
<th>Table 2. Summary of concomitant medications at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% of patients receiving):</td>
</tr>
<tr>
<td>Infliximab dose</td>
</tr>
<tr>
<td>All Patients</td>
</tr>
<tr>
<td>Number (%) of patients</td>
</tr>
<tr>
<td>n=6 n=7 n=8 n=21</td>
</tr>
<tr>
<td>1 mg/kg 5 mg/kg 10 mg/kg</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>≤20 mg/day 3 (50.0) 5 (71.4) 2 (33.3) 10 (52.6)</td>
</tr>
<tr>
<td>&gt;20 mg/day 3 (50.0) 2 (28.6) 4 (66.7) 9 (47.4)</td>
</tr>
<tr>
<td>Rectal 2 (33.3) 1 (14.3) 0 (0.0) 3 (14.3)</td>
</tr>
<tr>
<td>6-Mercaptopurine or Azathioprine</td>
</tr>
<tr>
<td>Methotrexate 0 1 (14.3) 2 (25.0) 3 (14.3)</td>
</tr>
<tr>
<td>Oral aminosalicylates 5 (83.3) 6 (85.7) 6 (75.0) 17 (81.0)</td>
</tr>
<tr>
<td>Antibiotics 2 (33.3) 4 (57.1) 1 (12.5) 7 (33.3)</td>
</tr>
</tbody>
</table>
### Table 3. Number (%) of patients achieving clinical response and clinical remission* over time.

<table>
<thead>
<tr>
<th>Infliximab dose</th>
<th>1 mg/kg (n=6)</th>
<th>5 mg/kg (n=7)</th>
<th>10 mg/kg (n=8)</th>
<th>Patients (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical remission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>0/5 (0.0)</td>
<td>6/7 (85.7)</td>
<td>8/8 (100)</td>
<td>19/20 (95.0)</td>
</tr>
<tr>
<td>Week 2</td>
<td>0/6 (0.0)</td>
<td>5/6 (83.3)</td>
<td>7/8 (87.5)</td>
<td>17/20 (85.0)</td>
</tr>
<tr>
<td>Week 4</td>
<td>1/6 (16.7)</td>
<td>6/6 (100)</td>
<td>5/6 (82.5)</td>
<td>15/18 (83.3)</td>
</tr>
<tr>
<td>Week 8</td>
<td>1/5 (20.0)</td>
<td>4/5 (80.0)</td>
<td>5/6 (82.5)</td>
<td>12/18 (66.7)</td>
</tr>
<tr>
<td>Week 12</td>
<td>0/4 (0.0)</td>
<td>3/7 (42.9)</td>
<td>5/7 (71.4)</td>
<td>11/18 (61.1)</td>
</tr>
<tr>
<td><strong>Clinical response</strong></td>
<td>6/6 (100)</td>
<td>7/7 (100)</td>
<td>8/8 (100)</td>
<td>21/21 (100)</td>
</tr>
<tr>
<td>Week 1</td>
<td>5/5 (100)</td>
<td>6/6 (85.7)</td>
<td>7/8 (87.5)</td>
<td>19/20 (95.0)</td>
</tr>
<tr>
<td>Week 2</td>
<td>5/6 (83.3)</td>
<td>5/6 (83.3)</td>
<td>4/6 (66.7)</td>
<td>17/20 (85.0)</td>
</tr>
<tr>
<td>Week 4</td>
<td>5/6 (83.3)</td>
<td>6/6 (100)</td>
<td>5/6 (82.5)</td>
<td>15/18 (83.3)</td>
</tr>
<tr>
<td>Week 8</td>
<td>3/5 (60.0)</td>
<td>4/5 (80.0)</td>
<td>5/7 (71.4)</td>
<td>12/18 (66.7)</td>
</tr>
<tr>
<td>Week 12</td>
<td>3/4 (75.0)</td>
<td>3/7 (42.9)</td>
<td></td>
<td>11/18 (61.1)</td>
</tr>
</tbody>
</table>

*Clinical response was defined as improvement from baseline of ≥10 points on the PCDAI; clinical remission was defined as a PCDAI <10.

### Table 4. Median endoscopic lesion severity score at baseline and Week 4

<table>
<thead>
<tr>
<th>Infliximab dose</th>
<th>1 mg/kg (n=3)</th>
<th>5 mg/kg (n=3)</th>
<th>10 mg/kg (n=3)</th>
<th>Patients (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>7.9</td>
<td>10.0</td>
<td>5.8</td>
<td>8.5</td>
</tr>
<tr>
<td><strong>Week 4</strong></td>
<td>4.5</td>
<td>2.6</td>
<td>1.1</td>
<td>2.6</td>
</tr>
</tbody>
</table>
Efficacy. Improvements in the PCDAI and ESR were observed with all infliximab doses beginning at Week 1, as displayed in Figure 1. Similar results were observed for CRP. On average, all treated patients experienced approximately 53% improvement in the median PCDAI by Week 2. By Week 12, the PCDAI remained approximately 30% improved from baseline. During the trial, all 21 (100%) patients achieved a clinical response (defined as improvement from baseline of ≥10 points on the PCDAI at some point during the observation period), and 10 of the 21 (47.6%) patients achieved clinical remission (defined as a PCDAI <10). The proportions of patients achieving clinical response and clinical remission are summarized by evaluation time point in Table 3. As displayed in Figure 1, the vast majority of patients achieved a clinical response by Week 1 (95.0%, 19/20 patients evaluated). The clinical response to infliximab was relatively durable through Week 12, and there was no difference among the infliximab dose groups in the achievement of a clinical response. The 5- and 10-mg/kg infliximab doses appear to be more effective than the 1-mg/kg dose in achieving clinical remission.

Nine patients were endoscopically examined prior to infliximab infusion and again at Week 4. The median endoscopic lesion severity scores improved by 43%, 74%, and 81% in the infliximab 1, 5, and 10 mg/kg groups, respectively (Table 3). Figure 2 illustrates the degree of correlation between the change from baseline in the endoscopic lesion severity score and the PCDAI.
Figure 1. Mean percentage improvement from baseline in median PCDAI (A), mean percentage of patients with clinical response (B), mean percentage improvement from baseline in median ESR (C) over time.

A. PCDAI improvement

B. Patients with clinical response

C. Percentage of ESR improvement
Figure 2. Correlation between change from baseline in endoscopic lesion severity score and PCDAI

![Graph showing correlation between change from baseline in endoscopic lesion severity score and PCDAI. The correlation coefficient (r) is 0.78 and the p-value is 0.024. The graph includes data points for different dosages: 1 mg/kg, 5 mg/kg, and 10 mg/kg.]

Figure 3. Mean serum infliximab concentrations over time

![Graph showing mean serum infliximab concentrations over time for pediatric and adult patients. The graph includes data points for different dosages: 1 mg/kg, 5 mg/kg, and 10 mg/kg.]

Pediatric: 1 mg/kg, 5 mg/kg, 10 mg/kg
Adult: 1 mg/kg, 5 mg/kg, 10 mg/kg
Safety. Four patients (19.0%) experienced an adverse event considered to be reasonably-related to study drug by the investigator; there was no evidence of a dose-relationship in the incidence of these adverse events. One patient in the 1-mg/kg group reported upper respiratory tract infection, and three patients in the 5-mg/kg group experienced upper respiratory tract infection, pancreatitis, and sinusitis/appendicitis. No infusion reactions (defined by occurrence during or within 1 hour following infusion) were reported.

During the 20-week study, no patient developed antibodies to dsDNA or antibodies to infliximab.

Pharmacokinetic assessments. Mean infliximab concentrations are displayed in conjunction with pharmacokinetic concentrations obtained from adult CD patients in Figure 4. These results indicate that serum infliximab concentrations are proportionate to dose, and that the pharmacokinetic profile in pediatric patients is similar to that in adults. Serum infliximab concentrations were detectable through Week 4 in the 1-mg/kg group, Week 8 in the 5-mg/kg group, and Week 12 in the 10-mg/kg group.

Discussion and conclusions

Given the morbidity associated with poorly controlled CD and the complications of long-term corticosteroid therapy in children, newer treatment strategies are needed. Results of studies involving the effect of anti-TNFα agents in adults with inflammatory bowel disease indicate that some of the same factors initiating the inflammatory response may also apply to children with CD. TNFα has multiple biologic activities. Relevant to CD is the capacity of TNFα to upregulate adhesion molecule expression, attract circulating inflammatory cells to areas of inflammation, activate the coagulation cascade, induce edema, participate in granuloma formation, and alter intestinal permeability.\textsuperscript{11, 12}
The profound benefit achieved in clinical trials in adult patients with CD prompted this evaluation of three infliximab doses in 21 CD patients between the ages of 11 and 17 years. The trial was open-label with regard to treatment, but double-blind with regard to dose level. The patient population evaluated had moderate to severe disease and, consistent with current management protocols for children with CD, a history of either corticosteroid or other immunosuppressant therapy. During the trial, all 21 (100%) patients achieved a clinical response, and the vast majority of patients achieved this response by Week 1. The clinical response to infliximab was relatively durable through Week 12, despite the protocol-specified reduction in steroid dose beginning at Week 4, and there was no difference among the infliximab dose groups in the achievement of a clinical response. Thus, the results of this study show that infliximab provides a dramatic benefit in pediatric CD patients refractory to standard medical therapy. This degree of clinical benefit has the potential to significantly reduce the requirement for steroid and immunomodulatory use. Taken together with the recent open-label experiences in pediatric CD\textsuperscript{9,10}, it is now becoming apparent that intervention with infliximab may lessen the occurrence of impaired growth and osteoporosis, and thus improve self esteem and quality of life, in pediatric CD patients.

The clinical benefit in children may in fact be even more profound than observed in a similar infliximab trial conducted in adult CD patients\textsuperscript{7}. Based on the differences in the mean duration of disease (4.0 years for the current trial compared to 12.5 years in adult CD patients), these observations may indicate that shorter disease duration correlates with the likelihood of clinical response. Conversely, it may be that children are more responsive to TNF blockade. Larger trials are required to further evaluate the actual degree of clinical benefit afforded by infliximab to pediatric CD patients.

Based on data obtained in this study and in a comparable trial conducted in adult CD patients\textsuperscript{7}, the pharmacokinetic profile of infliximab in pediatric patients with CD is similar to that in adults. While the small number of participants in this trial, descriptive nature of the data analyses, and lack of a placebo
comparator limit the conclusions that can be made, all doses of infliximab resulted in achievement of clinical response. The 1 mg/kg dose appears to produce a less durable response than the 5 and 10 mg/kg doses based on a lower overall clinical remission rate and lower serum infliximab concentrations over time. While this trial was not designed to establish the effective dose of infliximab in a population of children with CD, the consistency of the pharmacokinetic data with that of adults with CD indicates that the 5 mg/kg dose recommended for adults is probably the appropriate dose for children as well. Furthermore, infliximab was well tolerated with no infusion reactions in any of the treatment arms.

The benefits observed in this double-blind controlled trial suggest that infliximab may be an option for short-term treatment of active moderate to severe CD in pediatric patients. Further studies are recommended to determine the long-term safety and efficacy of infliximab in children with CD.
Acknowledgements

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References


