Early Mucosal Healing with Exclusive Enteral Nutrition is Associated with Improved Outcomes in Newly Diagnosed Children with Luminal Crohn’s disease

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Abstract

Background: Exclusive Enteral Nutrition (EEN) induction in children with luminal Crohn’s disease (CD) gives early mucosal healing (MH), but the long-term benefits of EEN-induced MH are just emerging.

Aims & Methods: We prospectively followed an Australian cohort of newly diagnosed children with predominantly luminal CD who completed at least six weeks EEN and with paired clinical Pediatric Crohn’s Disease Activity Index (PCDAI), biochemical (C-reactive protein; CRP) and endoscopic assessment at diagnosis and post EEN. All commenced immunomodulators (IMs) early (<3 months from diagnosis) and had a minimum of 1 year follow-up. Complete MH was a simple endoscopic score for Crohn’s disease (SES-CD) of 0, and SES-CD≥1 was ascribed to active endoscopic disease (aED) and further divided into near complete MH (SES 1–3), mild active disease (SES-CD 4–10) and moderate to severe disease (SES-CD>10). The primary outcome was long-term supervised sustained remission (SR) on IMs alone without need for corticosteroids, infliximab (IFX) or surgery.

Results: A total of 54 eligible children (33 males) completing EEN induction were analysed. The median duration between pre and post EEN assessments was 60.5 days [interquartile range (IQR), 56–69.5]. Post EEN: clinical remission (PCDAI < 10) was observed in 45/54 (83%), and biochemical remission (PCDAI < 10 and CRP < 5 mg/dl) was observed in 39/54 (72%). Complete MH was observed in 18/54 (33%), near complete in 10/54 (19%). SR was superior in those with complete MH vs. aED; 13/18, (72%) vs. 10/36 (28%), \(p = 0.003\) at 1 year, 8/16, (50%) vs. 3/24, (8%), \(p = 0.008\) at 2 years and (8/16, (50%) vs. 1/19, (6%), \(p = 0.005\) at 3 years. Near-complete MH did not lead to superior SR.

Conclusions: Only complete MH post EEN induction predicts more favourable SR for up to 3 years.

Key Words: EEN; mucosal healing; simple endoscopic score for CD

Abbreviations: aED, active endoscopic disease; CD, Crohn’s disease; CI, confidence interval; CRP, C-reactive protein; CS, corticosteroid; EEN, exclusive enteral nutrition; IFX, infliximab; IM, immunomodulator; IR, intestinal resection; IQR, interquartile range; MH, mucosal healing; NCH, near complete healing; PCDAI, Pediatric Crohn’s Disease Activity Index; SES-CD, simple endoscopic score for CD; SR, sustained remission; TNF, tumour necrosis factor; TP, thiopurine; TPMT, thiopurine methyltransferase.
1. Introduction

Therapies capable of inducing and maintaining endoscopic mucosal healing (MH) in Crohn’s disease (CD) are vital since adult data confirm rapid early and sustained MH in CD is associated with less frequent clinical relapses, fewer hospitalizations and reduced surgical resections.1-4 Paediatric studies prospectively comparing long-term outcomes based on endoscopic MH are limited, but suggest a positive impact of early MH on longer-term outcomes.5-8 Anti-tumour necrosis factor (anti-TNF) agents are widely used for induction and maintenance of remission in CD, and a range of step-up and step-down strategies have emerged, depending on availability and funding in each community. In Australia, government funding for anti-TNF agents for luminal CD is predicated on failure to respond to exclusive enteral nutrition (EEN) or corticosteroids (CSs) and at least 3 months of standard dosing with immunomodulators (IMs). Infliximab (IFX) had been the sole approved anti-TNF for luminal CD in children until September 2015. In our unit over the past 5 years, EEN has been the primary induction therapy for the majority of children, and IFX has been employed as early as 3 months, or soon after, for those failing EEN induction or relapsing on dose-optimized IMs. IFX-free sustained remission (SR) is therefore an excellent, additional proxy of long-term remission post EEN and is described in this cohort. We evaluated the impact of early EEN-induced MH for predicting SR on IMs without need for additional therapy such as CSs, IFX or intestinal resection (IR).

2. Methods

This study cohort is an extension of our previously described prospective study (Australia New Zealand Clinical Trials Registry – ACTRN12612001032842) of newly diagnosed children with predominantly luminal CD (<16 years) treated with EEN and early thiopurines (TPs) (<3 months from diagnosis).7 Institutional Ethics approval was granted and written consent obtained from patients and parents. Children completing at least 6 weeks EEN from November 2009 – November 2014, with a minimum of 12 months follow-up and complete paired clinical, biochemical and endoscopic assessment before and after EEN were included. A total of 12 children were excluded (9 without paired endoscopy, 2 with incomplete follow-up endoscopy and 1 with isolated proximal small intestinal CD). Phenotype data, including patient characteristics (endoscopy, radiology, biochemical, concurrent treatments and outcomes), were prospectively collected. Thiopurines (TPs) were initiated in all children, aiming for azathioprine (AZA) 2–2.5 mg/kg/day or 6-mercaptopurine 1–1.5 mg/kg/day, modified according to thiopurine methyltransferase (TPMT) status and targeting 6TG levels >2.50 pmol/8 × 10⁹ RBC. The 6 TGN level was measured at least twice in the first year after diagnosis and at least annually thereafter, as clinically indicated.

Clinical remission was defined as Paediatric Crohn’s Disease Activity Index (PCDAI) ≤ 10; biochemical remission, C-reactive protein (CRP) < 5 mg/L with PCDAI ≤ 10.9-11 Endoscopic response was determined by the endoscopist at the time of the procedure using the validated simple endoscopic activity score (SES) for CD; complete MH was SES-CD = 0, and SES-CD ≥ 1 was considered active endoscopic disease (aED). Active endoscopic disease was further subclassified as: near-complete MH (SES 1–3), mild active disease (SES-CD 4–10) and moderate to severe active disease (SES-CD > 10).12-13 Sustained remission was defined as supervised remission on IMs alone without documented relapse. Relapse was defined as elevated PCDAI > 15 and CRP > 5 mg/dL and/or faecal calprotectin > 250 mg/g stool and/or endoscopically or radiologically confirmed, leading to IFX, CS or surgery. Management of children relapsing during and after EEN induction on maintenance IMs was at the discretion of the treating gastroenterologist. Data on sustained CS/IFX/surgical–free remission was collected on children completing from 1 year to 4 years of follow-up, and the impact of post-EEN endoscopic score on SR was evaluated. Survival analysis was performed using Kaplan–Meier plots; time to relapse and time to IFX were measured separately against early MH and endoscopic responses as an additional proxy of long-term remission.

2.1. Statistics

All statistical calculations were performed using IBM SPSS ver. 22 and Graph Pad Prism Software. Descriptive data is reported as an interquartile range (IQR). Categorical and continuous data were analysed using the Fisher exact, Chi square and unpaired t tests. Baseline phenotype, laboratory and endoscopy variables pre- and post-EEN induction were compared between children with sustained remission vs. relapse and those with early MH vs. aED. Kaplan–Meier survival analysis was performed to evaluate time to relapse (mandating IFX or CS or surgery) and time to IFX based on post-EEN endoscopic outcomes. A Cox regression analysis was done to compare the hazard risk in those with clinical remission vs. biological remission vs. complete MH following a course of EEN.

3. Results

A total of 54 children (33 males) completing EEN induction with paired clinical, biochemical and endoscopy data with a median follow-up of 46 months [95% confidence interval (CI) 36–46] were analysed. Follow-up assessment, including endoscopy, was undertaken after the induction course of EEN. While aiming for repeat endoscopy after an 8-week EEN treatment course, as outlined in our previous publication, we included children with a minimum period of 6 weeks EEN and children whose follow-up endoscopy was delayed for several days to accommodate practical issues. The median duration of EEN was 8.57 weeks (IQR 7.7–9.5 weeks), and the median time between pre- and post-EEN assessment was 8.6 weeks (IQR 8–10 weeks).

3.1. Time to follow-up endoscopy after the course of EEN in those with active vs. inactive clinical disease were similar (55 vs. 61 days, p = 0.2)

After completion of EEN, 45 (83%) were in clinical remission; 39 (72%) in biochemical remission; 18 (33%) children had complete MH (SES = 0); 10 (19%) near-complete healing (NCH) (SES 1–3); 26 (48%) had incomplete healing, with mild disease activity in 17 (31%) and moderate disease activity in 9 (17%). Over 3 years, 45/54 (83%) of children relapsed and were managed with IFX (n = 39, 72%), intestinal resection (n = 3), intestinal resection and IFX (n = 2) and CS (n = 1).

3.2. Comparison of clinical characteristics and outcomes for those with complete mucosal healing (SES-CD 0) vs. active endoscopic disease (SES-CD > 1)

Clinical characteristics at diagnosis and post-EEN induction were comparable in children with complete MH compared with aED, except that those with complete MH had a greater overall drop in mean PCDAI and CRP and a higher proportion of children with CRP normalization (<5 mg/dL) (Table 1). Greater sustained remission was observed at 1, 2 and 3 years in those achieving complete MH vs. aED post EEN. (Figure 1) Kaplan–Meier survival analysis confirmed both a greater relapse-free survival (supervised remission not requiring CS, IFX or IR) and IFX-free remission in those with early MH vs. aED. (Figures 2, 3).
3.3. Predictors of sustained remission
Sustained remission at 1, 2 and 3 years after EEN induction and early IMs was observed in 23/54 (42%), 11/40 (27.5%) and 9/35 (26%), respectively. Baseline clinical and phenotypic characteristics were similar between groups in SR vs. Relapse at 1 year, apart from a greater mean improvement in SES-CD at post-EEN endoscopy in those with SR (Table 2). We also evaluated the discriminative value of post-EEN induction clinical vs. biochemical remission vs. endoscopic healing in predicting sustained remission using Cox regression analysis. Only MH, not clinical or biochemical remission, predicted a superior sustained remission (Table 3). Quality of post-EEN MH (SES-CD) was also measured against the risk of subsequent relapse. Only complete MH SES-CD = 0 reliably predicted a greater relapse-free survival at 1, 2 and 3 years compared with those with NCH vs. mild active disease vs. moderate active disease (Figure 4).

3.4. Outcome of the children excluded from the study
A total of 12 children were excluded due to lack of or incomplete post-induction endoscopy. Those achieving SR at 1, 2 and 3 years...
after EEN induction and early IMs for those excluded from the study and without endoscopic response for subclassification were 6/12 (50%), 3/8 (37%) and 2/7 (28%), respectively.

4. Discussion
This is the largest prospective longitudinal cohort study confirming improved long-term outcomes in newly diagnosed children with luminal CD achieving early complete MH on EEN. We have also again demonstrated that control of symptoms, or improvement of serum biomarkers with clinical remission alone, are inferior compared with complete MH after EEN induction in predicting SR. Sustained remission was greatest in those achieving complete disappearance of ulcers. Near-complete MH did not give significantly improved SR over more active endoscopic disease.

Relapse was progressively more frequent in those with aED vs. complete MH; 26/36 (72%) vs. 5/18 (28%), p = 0.003 at 1 year, 21/24 (92%) vs. 8/16, (50%), p = 0.008 at 2 years and 18/19 (94%) vs. 8/16, (50%), p = 0.005 at 3 years.

Our findings that early complete MH is vital for optimizing subsequent clinical outcomes has support from recent studies. A placebo-controlled randomized control trial with adalimumab in adults with moderate–severe CD demonstrated the positive impact of early (12-week) complete MH (SES-CD = 0) on Week-52 outcomes. In this study, a ‘1-point increase in Week-12 SES-CD score was associated with a 5.0-point increase in Week-52 CDAI score (p < 0.05)’.
Conversely, higher Week-12 SES-CD scores were associated with a reduced Odds Ratio (OR) of 0.6, p < 0.05, of Week-52 remission.

Another recent paediatric anti-TNF cohort study with planned follow-up endoscopy at 9–12 months also reported the positive predictive value of complete MH, with 79% clinical remission rates at

Table 2. Comparison of demographic and clinical characteristics pre and post EEN between children with sustained remission vs. relapse in the first year.

<table>
<thead>
<tr>
<th></th>
<th>Sustained remission (n = 23)</th>
<th>Relapse (n = 31)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Mean age</td>
<td>11.9</td>
<td>12.8</td>
<td>NS</td>
</tr>
<tr>
<td>Females, (38%)</td>
<td>11</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Mean PCDAI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>37</td>
<td>39</td>
<td>NS</td>
</tr>
<tr>
<td>Post induction</td>
<td>4.9</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>42.3</td>
<td>43.3</td>
<td>NS</td>
</tr>
<tr>
<td>Post induction</td>
<td>4.42</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>CRP &lt; 5 mg/dL (78%)</td>
<td>20/23</td>
<td>22/31</td>
<td></td>
</tr>
<tr>
<td>SES-CD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>13.9</td>
<td>14.5</td>
<td>NS</td>
</tr>
<tr>
<td>Post induction</td>
<td>3.4</td>
<td>6.61</td>
<td>0.04</td>
</tr>
<tr>
<td>Disease phenotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileal (15%)</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Ileocolonic (74%)</td>
<td>18</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Colonic (11%)</td>
<td>2</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Disease modifier</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>UGI disease (59%)</td>
<td>14 (26%)</td>
<td>18 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Perianal disease (20.6%)</td>
<td>3 (5.6%)</td>
<td>8 (15%)</td>
<td></td>
</tr>
<tr>
<td>Complicating disease (B2/B3)</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Mean time from diagnosis to TP use</td>
<td>4.1 weeks</td>
<td>5.16 weeks</td>
<td>NS</td>
</tr>
<tr>
<td>Mean follow-up from diagnosis</td>
<td>48</td>
<td>39</td>
<td>0.05</td>
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</table>

Table 3. Cox regression analysis comparing post EEN clinical and biological remission vs. mucosal healing in predicting relapse.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>Significance</th>
<th>95% CI for Odds Ratio</th>
</tr>
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<tbody>
<tr>
<td>Mucosal healing</td>
<td>0.48</td>
<td>0.04</td>
<td>0.23–0.98</td>
</tr>
<tr>
<td>Biochemical remission</td>
<td>0.47</td>
<td>0.08</td>
<td>0.2–1.1</td>
</tr>
<tr>
<td>Clinical remission</td>
<td>0.71</td>
<td>0.53</td>
<td>0.24–2.06</td>
</tr>
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Figure 2. Time to relapse (months) between those with early complete mucosal healing vs. active endoscopic disease.

Figure 3. Time to infliximab (IFX; months) between those with early complete mucosal healing vs. active endoscopic disease.
2 years in those achieving complete MH vs. 67% with partial MH (SES-CD drop >50%).

Our early MH rates following EEN therapy are comparable (33%) with our previous reports of 44%. Our study is also the first to prospectively examine the impact of early EEN-induced MH on important real-life long-term clinical outcomes, i.e. need for infliximab, CsA or surgical resection in a well-characterized cohort with a consistent practice of diagnosing and management of CD relapse. In a previous retrospective study comparing EEN vs. CS-induced endoscopic remission, those with EEN-induced early endoscopic remission were less likely to relapse within 1 year (40%) compared with CS-induced endoscopic remission (70%).

Our study was not designed to address the impact of early IMs use on early MH or subsequent clinical outcomes. Most children commenced IMs at around 4 weeks, as has been common paediatric practice, and the delayed peak efficacy of TPs meant early use was unlikely to affect early endoscopic outcomes. However, recent adult controlled trials demonstrated early introduction of TPs did not improve outcomes, including maintenance of steroid-free remission, or need for anti-TNF or intestinal surgery. Our data supports this finding since the mean times to initiate IMs were similar in those with early MH vs. those with active endoscopic disease and in those with sustained remission vs. relapse, confirming that early use or otherwise of TPs is not as important as early MH.

A greater number of children with complete MH vs. aED demonstrated post-induction normalization of CRP (94% vs. 65%, p = 0.04); however, CRP value at diagnosis was higher in those with aED vs. complete MH (mean 50.6 vs. 31.5 mg/dL, p = NS), probably indicating greater inflammatory disease load.

We acknowledge that our longitudinal cohort study has limitations as an uncontrolled study, and in having a small sample size and the potential for bias. However, the potential for bias was low because the introduction of IFX to the cohort was predefined by government funding criteria. More importantly, escalation of treatment was not solely based on the presence of symptoms, but also on at least one abnormal objective biomarker of inflammation, including CRP, faecal calprotectin or repeat endoscopic or radiological evidence of relapse.

In our current study we did not examine serological immune response, genetic or microbiome signatures to predict disease course and/or therapeutic response, as suggested by recent data. Using a systems dynamic analysis approach, Dubinsky et al. confirmed that small bowel involvement, perianal disease and increased serological immune response are strongly associated with complicating paediatric CD. Recently, Haberman et al. also documented that microbial signatures from ileal tissue provided a modest predictive value, with higher APOA1 gene expression and Veillonella to Blautia ratio associated with a more sustained steroid-free remission. These observations suggest that further comprehensive studies are warranted combining detailed clinical, endoscopic, serological, genetic and microbiological signatures to predict disease outcomes.

In conclusion, we demonstrate that early complete MH post EEN induction predicts sustained remission over and beyond 3 years on maintenance IMs and that only complete MH (SES-CD = 0) provides improved outcomes. Our data also indicates that early MH may be more important than baseline disease severity or timing of IM introduction for predicting sustained anti-TNF/surgical–free remission of up to 3 years and beyond.

Funding
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Conflict of Interest
ZG has received lecture fees and conference registration from Janseen, Ferring and Abbvie Australia. PJL has received lecture fees. He is also a member of the scientific advisory board of Abbvie and Janssen Australia. RM, CB and CR declare that they have no conflicts of interest.

Author Contributions
ZG and PJL contributed to the study concept and design. ZG, CB, RM and CR contributed to acquisition of the data, ZG analysed the data and wrote the first draft and performed a critical revision of the manuscript. PJL contributed to the study supervision and revision of the MS. ZG and PJL obtained funding for the study.

References


