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Predictors of response to Infliximab in children with luminal Crohn's disease☆

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Abstract

Objective: A significant proportion of patients with initial response to Inflximab (IFX), subsequently lose response (LOR). Multicentre paediatric studies report LOR in 33% to 50% with 3–5 year follow-up. Our retrospective study examined durability of response and predictors of LOR.
Methods: From our IBD database of 185 children with CD, 65 received IFX maintenance therapy for luminal or fistulising Crohn's disease between January, 2006 and April, 2013. 47 with luminal CD ≥1 year follow-up after commencing IFX were included. We evaluated variables associated with response and describe outcomes on those remaining on IFX at four time points; before IFX, after induction, at 1 year and at the last follow-up. Response was divided into sustained primary, recovered, durable (combined sustained primary and recovered) and complete LOR (discontinuation from LOR or intolerance).
Results: Overall, 28/47 (60%) children sustained primary response over a median duration of 2.83 years (1.6–4.4, IQR). 19/47 (40%) developed LOR (including 2 intolerant) at a median of 11 months (9–19, IQR). Of 17 with LOR, 7 were successfully re-induced giving durable response (35/47, 74%); 6 failed dose intensification needing surgery (n = 2), second anti-TNF (n = 2) or both (n = 2). 4 had surgery without dose intensification.
LOR was associated with low BMI at diagnosis, lower height Z scores prior to induction, elevated CRP following induction (p = 0.007) and failure to use concomitant IM (p = 0.02).
Conclusion: The cumulative probability of durable response to IFX in luminal CD was 83%, 74% and 70% after 1, 2, and 3 years on IFX maintenance therapy.

1. Introduction

Crohn's disease (CD) is a chronic, debilitating gut disorder affecting growth, well-being, education, and employment and nearly 25% of patients are diagnosed before 16 years of

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age.[1] Paediatric onset CD is a more severe phenotype with the additional issues of growth failure, delayed puberty, reduced bone density and the consequences of a chronic disease commencing at a vulnerable period of psychosocial development.[2–7] Cohort studies comparing the clinical course of paediatric vs. adult onset CD confirms a more aggressive nature with extensive intestinal involvement, rapid progression and increased disease activity index, year by year, despite use of more immunosuppression.[8–10] The efficacy of Infliximab (IFX) for the maintenance of short and long term clinical remission in paediatric CD is well documented. However, a significant proportion of patients who initially respond to treatment, subsequently lose response (LOR) experiencing flare of symptoms.[11] In adults with CD, LOR affects 13% per patient year and associated with longer disease duration (>2 years), stricturing behaviour, smoking, high CRP, concomitant steroids & small bowel involvement.[12,13] Paediatric data from US and Europe multicentre cohort studies have observed loss of response to IFX in 33% to 50% with 3–5 year follow-up, with almost 50% requiring dose intensification (increased dose or frequency) during maintenance therapy.[14–17] The heterogeneity in study design and definitions of loss of response, the differences of induction therapies and IFX eligibility criteria internationally all demand the need for a specific appraisal of IFX outcomes in our cohort of Australian children. There are no published Australian data on long term safety and efficacy of IFX therapy in paediatric CD. The purpose of our retrospective single centre cohort study was to examine the durability of response and predictors of loss of response to IFX.

2. Material and methods

2.1. Patients and study design

The Brisbane Paediatric Inflammatory Bowel Disease database has been a major initiative for collecting IBD data both retrospectively and prospectively since 2005, as part of an ethically-approved longitudinal audit of the natural history and genetics of CD and UC at Royal Children's Hospital (RCH). RCH is a tertiary paediatric referral hospital providing services to Queensland and northern New South Wales with an estimated population of children (under 15) of 1 million. From our IBD database of 185 children with CD, we identified 65 patients who received IFX maintenance therapy for luminal or fistulising Crohn's disease between January, 2006 and April, 2013. IFX was accepted on the Pharmaceutical Benefits Scheme (PBS) for Australian children aged 6–17 years with confirmed CD in 2007 and access restricted to those with: complex perianal fistulising disease, Paediatric clinical disease index activity (PCDAI) ≥30 having failed adequate conventional therapy unless contraindicated. Conventional therapy is defined as 8 weeks of Exclusive Enteral Nutrition OR 6 weeks of tapering 1 mg/kg prednisolone AND ≥3 months of Imuran ≥2 mg/kg/day or 6-mercaptopurine ≥1 mg/kg/day or methotrexate ≥10 mg/m2. Approval to continue IFX is restricted to those with ≥15 base points improvement in PCDAI with total <30 or marked reduction (≥50%) in drainage or number of open perianal fistula assessed 4–6 weeks after third Induction dose IFX. IFX dose of 5 mg/kg to the nearest 100 mg was permitted under PBS criteria in addition it also requires six monthly prospective clinical and laboratory reporting for maintaining ongoing eligibility. This and other phenotype data including patient characteristics: endoscopy, radiology, biochemistry, concurrent treatments and outcomes were retrieved from our prospectively collected IBD database. Children with primary response to IFX for luminal CD and at least 1 year follow-up after IFX commencement were included. The aims of our study were to evaluate clinical and treatment related variables associated with IFX response and loss of response and quantify clinical outcomes on those remaining on IFX at four time points; before IFX, 4–6 weeks following IFX induction, at 1 year and at the last follow-up. We have used standard definitions but modified and enlarged these definitions for clarity of assessment.

Study definitions:

1. *Infliximab response* was defined as an improvement in symptomatic inflammatory activity (>15 point drop in PCDAI/PCDAI < 30 with or without normal CRP < 5 mg/L).
   Primary response to induction therapy was assessed at 4–6 weeks after 3rd dose IFX (0, 2, 6 weeks).
   Primary non-response: was defined as no improvement in symptomatic inflammatory activity at 4–6 weeks after 3rd induction dose.
   Secondary loss of response: was defined as symptomatic inflammatory relapse (PCDAI > 30 with elevated CRP or Calprotectin and/or endoscopically or radiologically confirmed relapse after successful primary response.
   This was further subdivided into *recovered response* (those recovering response after IFX dose intensification) or *complete loss of response* as discontinuation due to intolerance or failure to recover response after dose intensification and requiring second anti-TNF agent or surgical excision or both.
   Sustained primary response: was defined as clinical response on IFX maintenance not requiring dose intensification, surgical excision or second anti-TNF use.
   Durable response: was defined as the combination of *sustained primary response* and *recovered response*, successfully maintained on IFX.
2. Steroid use
   Steroid free remission: no concurrent steroids to maintain clinical remission.
   Steroid dependency: >3 months ≥ 0.5 mg·kg·day or 10 mg/day prednisolone or clinical relapses within 3 months of tapering steroids.[18]
3. Clinical characteristics
   Clinical phenotype was defined using Modified Montreal/Paris classification. Height Z scores −1.64 corresponding to <5th percentile was denoted as the presence of growth failure.[5,19] BMI Z scores were calculated using Center for Disease Control (CDC) growth charts and BMI Z scores < −1, <−2, <−3 defined as grade 1, grade 2 and grade 3 thinness respectively based on international expert guidelines.[20] PCDAI >30 is moderate to severe paediatric CD.[21,22] Clinical remission PCDAI < 10; clinical response as drop in PCDAI of 15 points from the baseline and (≥50%) reduction in drainage or number of open perianal fistula. Biochemical remission as CRP < 5 mg/L and biochemical response as more than 50% drop in CRP from baseline.[23,24] Clinical relapse was defined as PCDAI > 15 on more than one occasion 1 week apart and/or CRP > 5 mg/L with clinically

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