Infliximab for intensification of primary therapy for patients with Kawasaki disease and coronary artery aneurysms at diagnosis

Koichi Miyata 1, Emelia V Bainto, Xiaoying Sun, Sonia Jain, Kirsten B Dummer, Jane C Burns, Adriana H Tremoulet

ABSTRACT

Objective Children with Kawasaki disease (KD) and an initial echocardiogram that demonstrates coronary artery aneurysms (CAAs, Z score ≥2.5) are at high risk for severe cardiovascular complications. We sought to determine if primary adjunctive infliximab treatment at a dose of either 5 or 10 mg/kg, compared with intravenous immunoglobulin (IVIG) alone, is associated with a greater likelihood of CAA regression in patients with KD with CAA at the time of diagnosis.

Design and setting Single-centre observational study.

Patients Children with acute KD and Z score ≥2.5 at baseline.

Interventions Primary adjunctive infliximab (5 or 10 mg/kg) within 48 hours of initiating IVIG 2 g/kg.

Main outcome measures Incidence of CAA regression to Zmax <2 within 2 months of disease onset.

Results Of the 168 patients with KD, 111 received IVIG alone and 57 received primary adjunctive infliximab therapy: 39 received 5 mg/kg and 18 received 10 mg/kg. Incidence of CAA regression to Zmax <2 within 2 months was statistically significant at 52%, 62% and 83% in the IVIG alone, IVIG+infliximab 5 mg/kg and IVIG+infliximab 10 mg/kg, respectively. The multivariable logistic regression model adjusting for age, sex, baseline Zmax and bilateral CAA at baseline showed that IVIG plus 10 mg/kg infliximab was significantly associated with a greater likelihood of CAA regression (adjusted OR: 4.45, 95% CI 1.17 to 16.89, p=0.028) compared with IVIG alone. The difference between IVIG+infliximab 5 mg/kg and IVIG alone was not significant.

Conclusions Primary adjunctive high-dose 10 mg/kg infliximab treatment was associated with a greater likelihood of CAA regression in patients with CAA at the time of diagnosis.

INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of unknown aetiology that predominantly affects children <5 years of age. KD is the most common cause of acquired heart disease in children in developed countries with increasing incidence in many parts of the world.1–3 About 5% of patients still develop medium or large coronary artery aneurysms (CAAs) despite timely administration of standard treatment with intravenous immunoglobulin (IVIG).4 Children with CAA may experience significant morbidity including myocardial infarction, arrhythmias or sudden cardiac death.5 Adjunctive therapies including corticosteroids, infliximab, etanercept, cyclosporine and anakinra combined with IVIG have been administered to reduce CAA.6–11 Infliximab, a chimeric monoclonal antibody that specifically binds tumour necrosis factor (TNF) α, has been shown to be safe and well tolerated.12–14 A randomised, placebo-controlled trial of infliximab plus IVIG for intensification of initial treatment showed that infliximab reduced fever duration and some markers of inflammation, but was not powered to show a difference in the rate of CAA between the groups.15 Several studies have established that the best predictor of subsequent CAA is a coronary artery Z score (internal diameter normalised for body surface area) ≥2 on the initial echocardiogram.16–20 Recent studies have suggested that primary adjunctive anti-inflammatory therapies improve coronary artery outcomes in patients with CAA at the time of KD diagnosis, but have not addressed the relationship between the dose of infliximab and coronary artery outcomes.21–22

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Children with Kawasaki disease (KD) and an initial echocardiogram that demonstrates coronary artery aneurysms (CAAs; Z score ≥2.5) are at high risk for severe cardiovascular complications and should receive adjunctive anti-inflammatory therapy as per the American Heart Association Scientific Statement.

WHAT THIS STUDY ADDS

- This single-centre cohort study of 168 KD children with Z≥2.5 at baseline is the first to demonstrate that intravenous immunoglobulin (IVIG) plus high-dose 10 mg/kg infliximab is significantly associated with a greater likelihood of CAA regression to Z<2 within 2 months of onset compared with IVIG alone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Primary adjunctive high-dose 10 mg/kg infliximab therapy rather than low-dose 5 mg/kg may benefit high-risk KD children with Z score ≥2.5 at baseline by improving coronary artery outcomes.

- Multicentre, randomised controlled trials are warranted to confirm the effect of primary adjunctive infliximab treatment for patients with KD with CAA at the time of diagnosis.
While the 2017 American Heart Association (AHA) Scientific Statement recommends that ‘patients believed to be at high risk for development of CAA may benefit from primary adjunctive therapy’ and infliximab at 5 mg/kg is provided as an option, few studies have evaluated primary adjunctive infliximab use in patients with KD presenting with CAA at diagnosis.\(^2\)\(^{2-}\)\(^{24}\) Furthermore, since publication of the need for a higher dose of infliximab at 10 mg/kg in patients with CAA based on a pharmacokinetic study,\(^2\)\(^5\) no study has compared 5 vs 10 mg/kg of infliximab in patients with KD.

In this single-centre study, we compared primary adjunctive infliximab treatment at a dose of either 5 or 10 mg/kg with IVIG alone for CAA regression in patients with KD with a coronary artery Z score of at least 2.5 SD units on their first echocardiogram at the time of KD diagnosis.

METHODS
Study design and population
We reviewed all children diagnosed with KD and treated at Rady Children’s Hospital San Diego, California, USA, from 1 July 1989 to 29 February 2020. The study included patients if they (1) were diagnosed within 10 days after fever onset, (2) had Z score ≥2.5 for the right coronary artery (RCA) or left anterior descending coronary artery (LAD) at time of diagnosis on their baseline echocardiogram, (3) received IVIG (2 g/kg) and aspirin or primary adjunctive infliximab treatment (within 48 hours of initiating IVIG infusion). All subjects met the AHA definition for either complete or incomplete KD.\(^2\)\(^4\) Patients were excluded if they had recurrent KD or received any other additional anti-inflammatory therapies.

Treatment protocols
The treatment of patients with KD at our centre was determined by standardised protocols that changed over time. The standard treatment of all patients with KD was IVIG (Gammagard, Baxter Pharma) 2 g/kg IV and aspirin. In 2004, the treatment protocol was changed by adding 5 mg/kg infliximab following IVIG administration for most patients with CAA at diagnosis. There was still a cohort with small CAA through 2014 that received IVIG alone. As part of a clinical trial, a subset of patients treated with infliximab 5 mg/kg received this medication just prior to receiving IVIG.\(^2\)\(^2\)\(^3\)\(^5\) Following completion in 2014 of a pharmacokinetic study of infliximab in the setting of IVIG infusion,\(^2\)\(^5\) the dose of infliximab was increased to 10 mg/kg. The dose of aspirin was initially 80–100 mg/kg/day until 2013 when the protocol was changed to 30–50 mg/kg/day. There are no data to suggest that aspirin at any dose has an effect on CAA. Aspirin was reduced to 3–5 mg/kg/day at the time of discharge from the hospital.

Data collection
Demographic and laboratory data, clinical information and echocardiogram results were prospectively collected and entered into a REDCap database. Patient height, weight and internal diameter of the RCA and LAD were recorded. Z scores (internal diameter normalised for body surface area) were calculated using the method of Dallaire and Dahdah\(^2\)\(^6\) for all echocardiograms. Zmax was defined as the highest Z score for the RCA or LAD. We analysed all echocardiograms at baseline and follow-up echocardiograms during the first 2 months after disease onset. We defined CAA regression as Z score <2 for both the RCA and the LAD as per the AHA guidelines.

Outcomes
The primary outcome measure was the incidence of CAA regression to Zmax <2 on the last echocardiogram within 2 months. We compared outcomes by treatment group: IVIG alone, IVIG plus low-dose infliximab (5 mg/kg) and IVIG plus high-dose infliximab (10 mg/kg)

Statistical analysis
Demographic and baseline characteristics were summarised and compared between the treatment groups. Three-group comparison used Kruskal-Wallis test for the continuous variables, while Fisher’s exact test was used for categorical variables. Outcome data were summarised and compared between the treatment groups. A logistic regression model was used to assess the treatment difference in CAA regression to Zmax <2 at the last echocardiogram within 2 months adjusting for age, sex, baseline Zmax and bilateral CAA at baseline. Adjusted ORs were presented with 95% CI. Statistical software R (V 4.1.2) was used for the analysis (http://www.r-project.org).

RESULTS
From 1 July 1989 to 29 February 2020, 1603 patients were treated for KD at Rady Children’s Hospital San Diego. Of these, 242 patients with KD met the entry criteria but 74 were excluded for receiving additional anti-inflammatory therapies. Therefore, the study included 168 children with a median age of 1.9 years (range: 0.1–11.4) and 76% were male. Of these, 111 (66%) received IVIG alone and 57 received primary adjunctive infliximab therapy: 39 (68%) received low-dose 5 mg/kg with 15 of those being treated with infliximab just prior to IVIG and 18 (32%) received high-dose 10 mg/kg infliximab with 4 of those being treated with infliximab just prior to IVIG (table 1). The IVIG-only group had baseline higher per cent immature neutrophils (bands) and lower per cent neutrophils. The group treated with IVIG plus infliximab 5 mg/kg was more likely to have bilateral CAA at baseline. Otherwise, demographic, laboratory and echocardiographic values did not differ among treatment groups. The severity of KD and coronary artery status were similar at baseline in the three groups.

Coronary artery outcomes are summarised in table 2. There was a statistically significant difference in CAA regression (Zmax <2) within 2 months across the three groups (IVIG alone: 52%, IVIG+infliximab 5 mg/kg: 62%, IVIG+infliximab 10 mg/kg: 83%, p=0.035). Coronary artery Z score at last follow-up within 2 months tended to be lower in the higher 10 mg/kg dose of infliximab group (IVIG alone: Zmax median 2.0 (IQR 1.5–2.5), IVIG+infliximab 5 mg/kg: 1.9 (1.3–2.3), IVIG+infliximab 10 mg/kg: 1.6 (1.4–1.8)), although the difference was not statistically significant (p=0.08). Similar trends were observed for the higher 10 mg/kg dose of infliximab with a greater decrease in Z score from baseline and fewer patients with persistent CAA (Zmax ≥2.5). The inclusion of patients with KD who met the entry criteria but received additional anti-inflammatory therapies along with infliximab still showed a significantly greater likelihood of CAA regression (Zmax <2) within 2 months across the three groups (IVIG alone: 47%, IVIG+infliximab 5 mg/kg: 61%, IVIG+infliximab 10 mg/kg: 69%, p=0.01). The multivariable logistic regression model compared primary adjunctive infliximab 5 mg/kg or 10 mg/kg to IVIG alone, adjusting for age, sex, baseline Zmax and bilateral CAA at baseline (figure 1). IVIG plus high-dose 10 mg/kg infliximab was significantly associated with a greater likelihood of CAA regression to Zmax <2 on the last echocardiogram within 2 months.
Original research

DISCUSSION

This single-centre study is the first to suggest that the addition of high-dose 10 mg/kg infliximab to initial IVIG therapy is associated with a greater likelihood of CAA regression in patients with CAA at the time of KD diagnosis.

According to the AHA KD guidelines, primary adjunctive therapy is suggested for patients who are believed to be at high risk for development of CAA. However, there has been lack of clarity regarding the definition of ‘high-risk KD patients’. Japanese investigators have focused on risk scoring systems to predict IVIG resistance and used these scores to identify patients who are candidates for primary adjunctive therapy. Clinical trials of intensification of IVIG therapy with either steroids or cyclosporine in Japanese children have shown a reduced risk of CAA. However, these scoring systems have poor predictive value performance in mixed ethnic populations in the USA. In addition, the Japanese risk scores were designed to identify patients at risk of treatment resistance, not CAA. Previous studies in mixed ethnic populations have demonstrated that Z score ≥ 2 at baseline is a significant predictor of future development.

Table 1  Baseline demographic and clinical characteristics by treatment group

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.0 (0.9–3.5)</td>
<td>1.6 (0.7–2.7)</td>
<td>1.5 (1.2–2.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Age &lt;1 year</td>
<td>31 (28)</td>
<td>16 (41)</td>
<td>3 (17)</td>
<td></td>
</tr>
<tr>
<td>Age &lt;5 month</td>
<td>14 (13)</td>
<td>6 (15)</td>
<td>2 (11)</td>
<td></td>
</tr>
<tr>
<td>Illness day*</td>
<td>6 (5–7)</td>
<td>6 (5–7)</td>
<td>5 (4–7)</td>
<td>0.38</td>
</tr>
<tr>
<td>Male sex</td>
<td>85 (77)</td>
<td>29 (74)</td>
<td>13 (72)</td>
<td>0.88</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Asian</td>
<td>32 (29)</td>
<td>11 (28)</td>
<td>4 (22)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>2 (2)</td>
<td>1 (3)</td>
<td>3 (17)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>24 (22)</td>
<td>4 (10)</td>
<td>6 (33)</td>
<td></td>
</tr>
<tr>
<td>More than one</td>
<td>14 (13)</td>
<td>7 (18)</td>
<td>6 (33)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (4)</td>
<td>1 (3)</td>
<td>3 (17)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>2 (11)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>34 (31)</td>
<td>15 (39)</td>
<td>5 (28)</td>
<td></td>
</tr>
<tr>
<td>Incomplete KD</td>
<td>29 (26)</td>
<td>6 (15)</td>
<td>6 (33)</td>
<td>0.23</td>
</tr>
<tr>
<td>Baseline WBC</td>
<td>13.8 (11.7–18.0)</td>
<td>16.7 (12.0–18.9)</td>
<td>12.3 (11.2–14.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>%Polys</td>
<td>50 (37–58)</td>
<td>57 (43–64)</td>
<td>53 (47–65)</td>
<td>0.041</td>
</tr>
<tr>
<td>%Bands</td>
<td>14 (7–23)</td>
<td>9 (3–18)</td>
<td>6 (3–12)</td>
<td>0.009</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>–1.7 (–2.5, –0.8)</td>
<td>–1.8 (–2.6, –1.3)</td>
<td>–1.5 (–2.8, –0.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Platelet count</td>
<td>404 (321–494)</td>
<td>410 (359–478)</td>
<td>371 (285–412)</td>
<td>0.12</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>8.3 (4.6–16.6)</td>
<td>8.7 (4.7–18.3)</td>
<td>7.0 (5.0–18.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>ESR (mm/hour)</td>
<td>65 (52–79)</td>
<td>66 (45–75)</td>
<td>66 (58–78)</td>
<td>0.85</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>39 (17–72)</td>
<td>43 (25–76)</td>
<td>45 (30–73)</td>
<td>0.38</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>49 (16–84)</td>
<td>66 (25–134)</td>
<td>28 (18–94)</td>
<td>0.19</td>
</tr>
<tr>
<td>Baseline LAD</td>
<td>3.0 (2.7–3.8)</td>
<td>3.1 (2.8–3.9)</td>
<td>3.0 (2.7–3.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Baseline Zmax‡</td>
<td>3.0 (2.7–3.8)</td>
<td>3.1 (2.8–3.9)</td>
<td>3.0 (2.7–3.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>CAA at baseline</td>
<td></td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Z 2.5 to 4.99</td>
<td>106 (96)</td>
<td>37 (95)</td>
<td>18 (100)</td>
<td></td>
</tr>
<tr>
<td>Z 5 to 9.99</td>
<td>4 (4)</td>
<td>2 (5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Z ≥10</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Bilateral CAA at baseline</td>
<td>12 (11)</td>
<td>14 (36)</td>
<td>1 (6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Date of the last follow-up echocardiogram</td>
<td>27 (14–41)</td>
<td>34 (23–40)</td>
<td>16.5 (11–27)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Data are median (IQR) or n (%). P value by Kruskal-Wallis test for continuous variables and Fisher’s exact test for categorical variables.

*First day of illness defined as first day of fever.
†SD units from the mean for age-adjusted haemoglobin values.
‡Zmax was defined as the highest Z score for RCA or LAD.

ALT, alanine aminotransferase; CAA, coronary artery aneurysm; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; GGT, γ-glutamyl transferase; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; LAD, left anterior descending coronary artery; Polys, polymorphonuclear leukocytes; RCA, right coronary artery; WBC, white blood cell.
of CAA. Ideally, additional anti-inflammatory therapy such as infliximab would be given prior to CAA formation. A clinical risk prediction model such as that developed by Son et al., which uses baseline demographic, laboratory and Z score data, can help identify such high-risk patients who warrant intensification of primary therapy. However, for those patients whose first echocardiogram already shows a Z score ≥2.5 of one of the coronary arteries, there is a lack of data as to which adjunctive anti-inflammatory therapies should be given to children with acute KD with CAA. A wide range of anti-inflammatory agents including corticosteroids, infliximab, etanercept, anakinra and cyclosporine have been advocated as adjunctive therapies. Serum levels of the pro-inflammatory cytokine TNFα are elevated during the acute phase of KD and are higher in patients who subsequently develop CAA. Therefore, blockade of TNFα with either infliximab, a chimeric monoclonal antibody that specifically binds TNFα, or etanercept, a soluble TNF decoy receptor, has been regarded as a logical approach. A randomised double-blind, placebo-controlled trial of 5 mg/kg infliximab plus IVIG for intensification of initial treatment enrolled 196 patients with KD. The study resulted in shorter fever duration and more rapid normalisation of C reactive protein, neutrophil count at 24 hours and erythrocyte sedimentation rate at week 2. The study also showed that patients who

<table>
<thead>
<tr>
<th>Coronary artery outcomes on the last echocardiogram within 2 months post-KD onset by treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIG n=111</td>
</tr>
<tr>
<td>Coronary artery Z score</td>
</tr>
<tr>
<td>LAD</td>
</tr>
<tr>
<td>RCA</td>
</tr>
<tr>
<td>Zmax*</td>
</tr>
<tr>
<td>Z score change from baseline</td>
</tr>
<tr>
<td>LAD</td>
</tr>
<tr>
<td>RCA</td>
</tr>
<tr>
<td>Zmax*</td>
</tr>
<tr>
<td>CAA regression Z&lt;2</td>
</tr>
</tbody>
</table>

Data are median (IQR) or n (%). P value by Kruskal-Wallis test for continuous variables and Fisher’s exact test for categorical variables. *Zmax was defined as the highest Z score for RCA or LAD.

CAA, coronary artery aneurysm; IVIG, intravenous immunoglobulin; LAD, left anterior descending coronary artery; RCA, right coronary artery.
received infliximab had a greater decrease in LAD Z score at week 2 although the study was underpowered to evaluate coronary artery outcomes.

Jone et al\(^2\) reported outcomes for patients presenting with CAA at a single centre who received intensification of initial therapy with 5 mg/kg of infliximab. Primary adjunctive infliximab therapy reduced the need for additional treatments compared with IVIG alone. However, there were no significant differences between treatment groups for length of stay, improvement in coronary Z scores or rate of decrease in C reactive protein. Dionne et al\(^2\) performed a retrospective analysis of high-risk North American patients with KD presenting with CAA at baseline who received either IVIG alone or primary adjunctive therapy with either infliximab (5 or 10 mg/kg) or corticosteroids. Intensification of initial therapy with either corticosteroids or infliximab was associated with a lower rate of subsequent CAA enlargement compared with IVIG alone.\(^2\)

At our centre, 10 mg/kg of infliximab has been used since 2014 based on the safety profile and the pharmacokinetics of infliximab modelled from two randomised studies in patients with KD. This study suggested that timing of infliximab administration relative to IVIG administration affects the distribution of the monoclonal antibody.\(^2\) The pharmacokinetic model predicted higher doses of infliximab would be required to achieve the same tissue concentrations compared with administration of infliximab in the absence of IVIG. Thus, an increase in the dose from 5 mg/kg to 10 mg/kg was warranted and was adopted as the standard dose of infliximab in KD for a recently completed clinical trial.\(^6\) Previous studies may have failed to demonstrate a benefit of primary adjunctive infliximab therapy due to the lower dose of 5 mg/kg.

Limitations

The data from this single-centre, retrospective observational study should be viewed as hypothesis-generating. To limit the conclusions to the effect of infliximab alone, the study excluded patients who received other additional anti-inflammatory treatments either as part of a clinical trial or as clinically indicated rescue therapies. This, in turn, limited our sample size. Another limitation is that the protocol-driven practice in our centre for high-risk patients evolved over time adding 5 mg/kg infliximab to IVIG in 2004, and then changing to 10 mg/kg infliximab in 2014. The technology and practice of echocardiograms varied over the period of the study. There may be unknown differences across the treatment groups in these different time periods. Finally, the sample size was relatively small, especially for the infliximab groups.

CONCLUSION

Primary adjunctive high-dose 10 mg/kg infliximab treatment was associated with a greater likelihood of CAA regression within 2 months in patients with CAA at the time of KD diagnosis. Multicentre, randomised controlled trials are warranted to confirm the effect of primary adjunctive infliximab treatment for patients with KD with CAA at the time of diagnosis.

Acknowledgements

KM would like to thank the travel grant for study abroad from Mitsukoshi Health and Welfare Foundation, Japan, which supported the travel expenses to San Diego. The sponsor had no role in the study.

Contributors

Concept and design: KM, AT, JCB; acquisition, analysis or interpretation of data: all authors; drafting of the manuscript: KM, AT, JCB; critical revision of the manuscript for important intellectual content: KM, KBD, AT, JCB; statistical analysis: KM, XS, SJ; administrative, technical or material support: EVB, AT, JCB; supervision: AT, JCB.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants and the collection of data was approved by the University of California San Diego IRB (#140220). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data sharing not applicable as no datasets generated and/or analysed for this study.

Supplemental material

This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID ID

Koichiro Miyata http://orcid.org/0000-0002-2049-5309

REFERENCES


Miyata K, et al. Arch Dis Child 2023;0:1–6. doi:10.1136/archdischild-2023-325639

Arch Dis Child: first published as 10.1136/archdischild-2023-325639 on 31 May 2023. Downloaded from http://adc.bmj.com/ on September 16, 2023 by guest. Protected by copyright.
Original research


