**Variation in access and prescription of vedolizumab and ustekinumab in paediatric inflammatory bowel disease patients: a UK-wide study**

Marcus KH Auth\*1, James J Ashton\*2,3, Kelsey DJ Jones4,5, Astor Rodriguess6, Dhamyanthi Thangarajah7, David Devadason8, Gemma Lee9, Mashhood Ayaz10, Huey Miin Lee11, Jochen Kammermeier9, **BSPGHAN IBD Biologics Survey Contributors**

BSPGHAN IBD Biologics Survey Contributors Group authors-

Kwang Yang Lee, Ewan Swann, Vikki Garrick, Franco Torrente, Protima Deb, Helen Doble, , Thankam Paul, Tracy Coelho, Veena Zamvar, Priya Narula, Andrew Fagbemi, Hemant S Bhavsar

\* Joint first authors

1. Department of Paediatric Gastroenterology, Alder Hey Children’s NHS Foundation Trust, Eaton Road, Liverpool, UK and University of Liverpool, UK
2. Department of Paediatric Gastroenterology, Southampton Children’s Hospital, Southampton, UK
3. Human Genetics and Genomic Medicine, University of Southampton, Southampton, UK
4. Department of Paediatric Gastroenterology, Great Ormond Street Hospital, London, UK
5. Kennedy Institute of Rheumatology, NDORMS, University of Oxford, UK
6. Department of Paediatric Gastroenterology, Oxford University Hospitals, Oxford, UK
7. Department of Paediatric Gastroenterology, Chelsea and Westminster Hospital, 369 Fulham Road, London, UK
8. Department of Paediatric Gastroenterology, Nottingham Children’s Hospital, Queens Medical Centre, Nottingham, UK
9. Department of Paediatric Gastroenterology, Evelina London Children’s Hospital, UK
10. Department of Paediatrics, Epsom and St Helier University Hospitals, UK
11. Department of Paediatric Gastroenterology, King’s College Hospital, London, UK

Correspondence to-

Marcus KH Auth, MD PD FRCPCH

Department of Paediatric Gastroenterology, Hepatology and Nutrition

Alder Hey Children’s NHS Foundation Trust,

Eaton Road,

Liverpool, L12 2AP

UK

Marcus.auth@alderhey.nhs.uk

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Contributorship

MA, JA and JK conceived the idea for the study and formulated the survey. The survey was distributed by JA. All contributors contributed data to the study by completing the online survey. Data were collated and analysed by JA and MA. Interpretation of data were led by JA, MA and JK with specific input from the IBD WG members (KJ, AR, GL, MA, DD, HML, DT). JA and MA wrote the manuscript with help from JK. All authors commented on, and approved, the article prior to submission.

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Abstract

Background– Therapeutic options for paediatric IBD are limited, especially for younger children. Unlike in adults, vedolizumab and ustekinumab are not licensed for paediatric use in the UK. We aimed to understand the real-world access to, and use of, these therapies in the paediatric population

Methods- We surveyed UK IBD centres to assess the incident use of vedolizumab and ustekinumab from 1/1/2021-31/12/2021. We collected information on funding, dose escalations and therapeutic drug monitoring (TDM).

Results- 18/21 centres responded, covering an estimated 5260 patients. One hundred and Thirteen were started on vedolizumab, prescription incidence 2.2%, median prescriptions per centre was 4 (range 1-20). Considering ustekinumab, 73 patients were commenced, prescription incidence 1.4%. Median prescriptions per centre was 3.5 (range 1-13). Prescription rates at each centre were not predicted by patient number cared for at that centre (p=0.2). Dose escalation was common in vedolizumab (66.7% centres) and ustekinumab (55.5%).

Funding strategies varied substantially, and multiple funding sources were used; 12/18 centres (66.7%) reported funding through routine NHS England/Scottish arrangements. There was local NHS trust funding in 8/18 centres (44.4%). Individual funding requests (IFRs) were used in 5/18 (27.8%), although IFRs are reserved for patients with unique additional characteristics. Four centres unable to achieve funding in pre-pubescent children.

Conclusions- There is widespread use of vedolizumab and ustekinumab across the UK, although practice is highly variable. Access to therapy appeared to differ substantially. There is a growing disparity between international guidelines and real-world practice. Establishing early and effective therapy in all patients remains a priority.

Introduction

Inflammatory bowel diseases (IBD), comprising Crohn’s disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU), are chronic inflammatory conditions resulting from a dysregulated immune system in the context of genetic predisposition and environmental triggers. Long-term treatment for paediatric-onset patients is limited to immune suppression through immunomodulators and anti-TNF monoclonal antibodies such as infliximab and adalimumab. Whilst these therapies are effective for many, up to 40% of patients will be primary non-responders to anti-TNF biologics and large numbers will have secondary loss of response to treatment [1]. Currently, funding for anti-TNF biologics is accessible via NHS England or alternative centralised funding processes in the devolved nations, such as the Scottish medicine consortium. In 2017, NHS England reviewed the evidence to treat patients aged under 18 years with additional medicines available for adults and concluded that there was enough evidence to consider making these treatments routinely available to patients aged less than 18 years in certain situations [2–4]. They concluded that safe and effective pharmacotherapy in paediatric patients required information on the proper use of products in various age ranges. NHS England followed a process introduced by the Federal Drug Administration (FDA) in 1994, in which data from adults were reviewed for extrapolation to children of five different age groups, with the last two age groups ranging from 2-11 years (children) and 12-18 years (adolescents). The NHS documents quoted FDA opinion that pharmacokinetic processes in adolescent patients were often similar to the pharmacokinetic processes in adults and monitoring the onset of puberty could be considered as a relevant threshold for determining whether an adult commissioning position could be extrapolated to a paediatric patient [3,4].

Vedolizumab, an anti- α₄β₇ integrin antibody, and Ustekinumab, an anti-IL12/23 antibody, appear to be effective and offer an alternative for paediatric patients not responding to first line treatment [5,6]. Whilst Vedolizumab and Ustekinumab appear to be effective in multiple paediatric cohort studies they are not licensed for children [7], and therefore funding for pre-pubertal patients will generally not be approved [8,9]. It remains comparatively difficult for paediatric data to meet standards for drug approval, specifically due to a lack of Phase III paediatric trials performed contemporaneously with adult studies [10,11]. In the case of Ustekinumab and Vedolizumab, phase III trials have only commenced in 2021 (UNIFI-jr and UNITI-jr) and 2021/2022, respectively.

Access to these medicines in an equitable and structured way is likely to provide improved outcomes for children and young people with IBD. Within nationally commissioned paediatric gastroenterology service there are quality standards aiming to reduce variation in care and ensure parity of access to services [12]. We aimed to gather real-world experience and collect evidence of access to vedolizumab and ustekinumab in paediatric IBD centres in the UK . Secondly, we assessed the ability of sites to prescribe and monitor these therapies for different age groups.

Methods

This study was conducted by of the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) IBD working group. Data were collected from sites across the United Kingdom.

Site selection

Twenty-one paediatric gastroenterology centres were identified across England, Wales, Scotland and Northern Ireland representing specialist centres for paediatric IBD (PIBD) as previously described [13]. An electronic survey was used to report experience. Each centre completed the survey only once. Patient numbers under the care of each site were derived from previously published data and were used to estimate prevalence of biologic prescription [13].

Survey questions

This survey was developed by the BSPGHAN IBD working group with a focus on reporting data on real-world practice and access to vedolizumab and ustekinumab, at a UK-wide level, for patients aged <18 years during the time-period 01/01/2021 to 31/12/2021. The questions were initially formulated by three member (JA, MA, JK) and iteratively discussed and refined with input from the IBD working group membership. The questions were informed through specialist pharmacy input and after discussion with representatives of the devolved nations within the UK.

Specifically, the survey aimed to gather information on:

1. How many patients were started on these medications and what age group did they fall into?
2. How has funding been obtained for different aged patients?
3. What dosage was used and which adjustments have been required?
4. Were any additional new generation biologics or small molecule therapies started in the 12-month period?

The full questionnaire is included as supplementary data 1.

Distribution of survey

Questions were entered into an online tool (Google Forms) and distributed to the lead PIBD contact at the 21 centres. We asked participants to report data on their PIBD centre (and their affiliated regional network hospitals) for the 12 months from the 1st of January 2021 to the 31st of December 2021. Participating centres were asked to consult with specialist pharmacists/nurse specialists to ensure data were accurate and complete. Responses were automatically stored and downloaded for analyses once all responses were collected.

Statistical and data analysis

Descriptive statistics were reported for all data. Factors associated with increased use of vedolizumab or ustekinumab were identified with multivariable regression analysis (SPSS v27, IBM).

Ethical approval

No patient identifiable data were collected. Consent was gathered from participation through the online survey and the study was not classified as research according to the Health Research Authority online decision tool.

Results

The survey was distributed to all centres and 18 of the 21 sites responded across England and Scotland. The PIBD population reported on has an approximate size of 5260 patients, with a mean PIBD cohort size of 290 patients per centre.

*Patients started on Vedolizumab*

A total of 113 patients were started on vedolizumab during the study period, representing an estimated prescription incidence of 2.2% of the total PIBD population. There was substantial variation between sites with the number of patients started on vedolizumab ranging from 1-20 [median: 4] patients per centre. New vedolizumab prescription rates at each centre varied from 0.3-4.4/100 patients per year. Figure 1A. Of those started on vedolizumab, 14 were biologic-naïve and 99 were switches from other monoclonals, all patient switches had previously had anti-TNF therapy and five of these patients were switched from ustekinumab.

Considering IBD diagnosis, 63.7% (n=72) of patients started on vedolizumab had a diagnosis of UC or IBDU, compared to CD who comprised 36.3% (n=41) of the starters. Ten of the 14 biologic-naïve patients had a diagnosis of UC. A total of 24 patients aged <13 years were started on vedolizumab, of which 18 (75%) had a diagnosis of UC or IBDU.

*Patients started on Ustekinumab*

A total of 73 patients were started on ustekinumab, equating to a prescription incidence of 1.4% of the PIBD population. Again, there was substantial variation in the number of prescriptions per centre, ranging from 1-13 patients [median: 3]. New prescription rates varied from 0.25-5.4/100 patients per year, figure 1B. Only 3 patients were previously biologic-naïve and all had a diagnosis of CD. All switches had previously had anti-TNF therapy, 11 patients had also had vedolizumab.

The majority of patients had a diagnosis of CD, 63/73, 86.3%. A total of 21 patients aged <13 years were started on ustekinumab during the study period of which 17 (81%) had a diagnosis of CD.

*Funding for therapies*

Funding strategies employed varied across the responding centres. All centres were able to get funding for at least one patient. Centres often had multiple funding methods for different patient groups. A total of 12/18 centres (66.7%) reporting they could get routine funding in post-pubescent patients for vedolizumab and ustekinumab through NHS England (blueteq) or similar central arrangements applicable for Scotland, through the Scottish Medicine Consortium. Local NHS trust funding was used in 8/18 centres (44.4%). Interestingly, NHS England individual funding requests (IFRs) had been used in five centres (27.8%). IFRs are reserved for patients with unique additional characteristics. A single centre was only able to use adult care arrangements and was therefore only able to use these medicines for patients aged >16 years of age.

Four centres (22.2%) reported being unable to achieve funding for ustekinumab or vedolizumab in children aged <13 years. Two centres reported NHS England funding for standard dosing of ustekinumab and vedolizumab, but for accelerated or increased dosing the cost was covered by the local NHS trust.

*Dosing and therapeutic drug monitoring (TDM)*

Considering vedolizumab in the study period, 12 centres (66.7%) had increased the dose or reduced the dosing interval in at least one patient. Considering ustekinumab, 10 of the 18 centres (55.5%) had increased or reduced dosing interval.

Eight centres (44.4%) were performing TDM for vedolizumab and four centres (22.2%) were performing TDM for Ustekinumab.

*Factors associated with increased prescriptions*

We performed multivariable regression analysis to identify factors associated with increased new generation monoclonal prescriptions. The number of vedolizumab and ustekinumab prescriptions were combined and assessed against each centre’s IBD population, funding sources available for that centre and ability to perform TDM. No factors significantly predicted number of new prescriptions- cohort size (p=0.2), local trust funding (0.36), NHS England or Scottish equivalent funding (p=0.91), or TDM (p=0.86).

Discussion

This study provides important evidence that specialist centres in the UK prescribe vedolizumab and ustekinumab in children and adolescents. Our national working group reports substantial variation in prescriptions of vedolizumab and ustekinumab across England and Scotland, with differing funding arrangements and access to those medicines. These variations do not meet equality principles as set out by NHS England and may affect health equalities and patient outcomes [2]. Moreover, some centres reported that they would have prescribed more patients these newer biologics if funding had been available. We provide the first evidence of the widespread use of these medicines in children from the UK, alongside dose escalation.

Although we have not collected further information on centre-specific patient phenotypes and disease severity, our data suggest significant variation in standard clinical practice given that the number of incident prescriptions was not predicted by the total number of PIBD patients cared for, although there may be a variation in case load severity between sites. Equally, funding opportunities varied widely across the surveyed centres. The decision from NHS England to grant funding for these medicines only to post-pubescent children may have contributed to variations in decision making.

Whilst there is a lack of clinical trial evidence, data from as far back as 2017 from the IBD PORTO group reported favourable outcomes in IBD patients from across different European countries, with different funding systems, although remission rates were relatively low at 37% in ulcerative colitis and 24% for Crohn’s disease [14]. Similarly, more recent observational data on 159 patients in an age range from 4-17 years, reported comparable remission rates of 43% at 1-year, with 86% of patients previously exposed to anti-TNF therapy [15]. A prospective study, ‘VEDOKIDS’, has recently reported and continues to indicate the usefulness of vedolizumab, especially in patients with ulcerative colitis [16]. A similar pattern is observed for ustekinumab, with 2019 data reporting on 44 children with Crohn’s disease refractory to conventional therapy with 38.6% reaching remission at 12 months [17]. Steroid-free remission was observed in 44% of ulcerative colitis patients treated with ustekinumab in a retrospective cases series of patients with previous biologic failures [18]. Significant delay in approving drugs for children with IBD, after therapies have already been approved for adult use, is well documented: Between 2005 and 2021, the EMA/FDA jointly approved two biologics for children with IBD compared to seven biologic drugs for adult patients [19]. The use of these biologics demonstrates similarities to the introduction of anti-TNF agents, with slower adoption prior to regulatory approval, followed by rapid expansion of prescription [20,21]. More recently, data appears to suggest that the more widespread adoption of anti-TNF therapy may be reducing the surgical resection rate during childhood, pointing towards the usefulness of standardised adoption of medication from both a patient and healthcare economic perspective [22].

When considering how best to use medications, adult studies continue to report the best outcomes for both vedolizumab and ustekinumab in patients who are biologic-naïve [23]. This poses further questions for standardisation of use in paediatric patients, where being able to select from any of the available biologic agents as first-line is not currently routinely possible in the UK. Further studies looking at optimal dosing strategies for different patient ages and disease subtypes are now starting to highlight some of the complexity in utilising these therapies to their maximal efficacy [24].

This study highlights different approaches to patients with IBD across the UK. Current international guidance for treatment of Crohn’s disease and ulcerative colitis reaches no firm conclusions for standardising when to use new generation therapies, with the use being ‘considered’ [25,26]. This study provides clear evidence of relatively widespread use with an estimated 3.6% of the prevalent paediatric IBD population surveyed being prescribed either vedolizumab or ustekinumab during the 12-month study period. Whilst caution should be exercised in the introduction of new medications, there is precedent for safe use of ustekinumab in younger children with psoriasis, where it is approved for use in those aged >6 years old.

The lack of equality in access to vedolizumab and ustekinumab was anecdotally known and is now evidenced. Funding strategies vary from centre to centre, and our data indicate some patients are unable to be escalated to vedolizumab or ustekinumab. Difficulty in funding therapy is established in insurance-driven healthcare but is relatively uncommon within the NHS [27]. IFR use was very limited and reflects patients with additional specific diseases or complications and is not a viable funding strategy for most patients with IBD. Undertreated IBD during childhood, especially in younger children, has significant health and economic consequences, which may be avoided with timely access to medication [28,29]. Timely and effective treatment in those children who are currently excluded from funding is extremely desirable.

This study has several strengths including wide coverage of patients across the UK and specific questions related to access and funding of medications, but we also acknowledge limitations. The purpose of this study was to provide real-world data on availability and prescribing practice for vedolizumab and ustekinumab monoclonal therapy in the UK and we specifically did not collect patient level data regarding prescriptions or reasons for prescriptions (including disease phenotype).

*Conclusions*

There is widespread use of new generation biologic therapy in paediatric IBD across the UK, but practice and access to therapy is highly variable. This has implications for individual patients and as our survey suggests at times for regional cohorts of patients within a national health service. There are age restrictions for some centres there is no ability to provide vedolizumab or ustekinumab to pre-pubescent patients, whereas other centres have been able to apply locally derived solutions. These data set out a current problem about equal access for biological treatments in children and young people [2].

We hope that these data will trigger discussions among decision-making bodies. Given the chronicity of IBD and risk of complications in this cohort acceptable and feasible solutions for funding and monitoring the use of vedolizumab and ustekinumab needs to be provided in children of all ages with IBD.

Figures

Figure 1A- Number of patients treated with vedolizumab compared to the total number of patients per centre, 1B- Number of patients treated with ustekinumab compared to the total number of patients per centre

“What is already known on this topic” –

* Therapeutic options for paediatric IBD are limited, especially for younger children
* Unlike in adult practice, newer biological therapies, vedolizumab and ustekinumab, are not licensed for paediatric use in the UK
* These therapies have evidence of benefit for paediatric patients of all ages

“What this study adds” –

* There is widespread use of vedolizumab and ustekinumab therapy in paediatric IBD across the UK
* Practice and access to therapy is highly variable between centres, with some having no ability to provide vedolizumab or ustekinumab to pre-pubescent patients
* These data set out the current issue of equitable access for biological treatments in children and young people

“How this study might affect research, practice or policy” –

* We hope that these data will trigger discussions among decision-making bodies.
* The importance of early and effective therapy in improving long term outcomes, especially in Crohn’s disease, underlines the need for access to contemporary therapy.
* We now need to find acceptable and feasible solutions for funding and monitoring the use of vedolizumab and ustekinumab for paediatric patients

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