EVIDENCE BASED CHILD HEALTH 4

Evidence in practice

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A clinical scenario is used to illustrate how the principles outlined in the previous articles in the series could be applied to help improve patient care. A practical demonstration of the art of formulating answerable clinical questions, finding evidence, critically appraising evidence, and putting evidence into practice is provided. The importance of integrating evidence with patient's preferences, and taking account of issues such as availability of interventions, costs, and so on is discussed. Finally, some of the issues involved in the development of evidence based policies within clinical teams are outlined.

CLINICAL SCENARIO

Laura, a 16 year old girl, was diagnosed with Crohn's disease 5 years earlier. Her disease was fairly well controlled in the first few years with intermittent use of corticosteroids, enteral nutrition, and mesalazine. In the past 6 months, however, she has been having persistent symptoms, and despite several courses of enteral nutrition and steroids together with immunosuppressive therapy (azathioprine), she remained quite unwell with bloody diarrhoea, abdominal pain, and marked weight loss. She was admitted to hospital with worsening symptoms and required treatment with intravenous steroids, with little benefit. Gastrointestinal endoscopies and barium imaging at this time confirmed severe extensive inflammation of the colon and small bowel. Laura's disease was clearly unresponsive to conventional treatment. Surgery was thought not to be an option because of the extensive nature of her disease. At one of their ward rounds, Dr B, specialist registrar in paediatrics told the consultant paediatrician that he had recently attended a meeting where he heard that a drug called infliximab could be useful in patients with Crohn's disease unresponsive to conventional treatment. The consultant asked Dr B to look for further evidence on the effectiveness of infliximab in the induction of remission in Crohn's disease. Dr B initially looked through his main paediatric gastroenterology textbook (published 7 years previously) for more information on this drug, but found nothing. He decided to investigate further for relevant evidence.

FOCUSED CLINICAL QUESTION

Dr B first decided to convert his information needs into an answerable clinical question. He had previously received some training in evidence based medicine (EBM) and knew that clinical questions are best formatted in the **PICO** or **PIO** format to include the **P**atient's problem or diagnosis; the **I**ntervention of interest, as well as any **C**omparison intervention (if relevant), and the **O**utcome of interest.[1]

His focused clinical question was therefore based on the following key elements arising out of his current information need:

- **Patient:** a 16 year old girl with active Crohn's disease unresponsive to conventional treatment
- **Intervention**: infliximab
- **Comparison:** no infliximab
- **Outcome:** induction of remission

These key elements were used to formulate the following clinical question:

In a 16 year old girl with active Crohn's disease unresponsive to conventional therapy, is infliximab effective in inducing remission?

SEARCH STRATEGY

As Dr B's question was about a treatment (an intervention), he was most interested in obtaining relevant systematic reviews of randomised controlled trials with or without meta-analysis, and randomised controlled trials (RCTs). He searched the following databases to which he had easy access at his hospital: the Cochrane database of systematic reviews, and Medline via PubMed.

Keywords needed for the search were drawn from the above focused clinical question. These were: Crohn's disease or its synonym Crohn disease; infliximab or its synonyms remicade and monoclonal antibodies cA2; and remission.

The following search strategy was used to search the Cochrane database of systematic reviews from the Cochrane Library (issue 4, 2004), and PUBMED (1966 to present) on the 28 December 2004: (1) Crohn's disease *or* Crohn disease; (2) infliximab *or* remicade *or* monoclonal antibodies cA2; (3) remission; (4): (1) *and* (2) *and* (3).

To make sure he was not missing any relevant systematic reviews, he also searched the ''clinical queries'' option for systematic reviews in PUBMED using the search strategy ''infliximab *and* Crohn's disease''.

Abbreviations: CDAI, Crohn's disease activity index; CDEI, Crohn's disease endoscopic index; EBM, evidence based medicine; RCT, randomised controlled trial; RR, relative risk; AR, absolute risk; ARR, absolute risk reduction; NNT, number needed to treat

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Results of the search

Cochrane library search

One relevant article was found in the Cochrane Database of Systematic Reviews.[2]

PubMed search

The main PubMed search initially yielded 125 articles. These were too many, so he limited the search further to try and retrieve the most relevant articles. Initially limiting the search to ''meta-analysis'', no article was obtained. He then limited the search to ''randomised controlled trials'', and 12 articles were retrieved. A quick glance at the titles or abstracts of these articles showed that only two of them were potentially relevant.[3 4] The rest were either narrative reviews, case series, or trials on the use of infliximab for other indications. However, he realised that the two articles identified had been incorporated into the systematic reviews identified from the Cochrane Library search and he decided that there was no need to collect those articles separately. The ''clinical queries'' search identified the systematic reviews already retrieved from the Cochrane library.

Summary of the systematic review

After reviewing a number of articles, the authors of the systematic review included one RCT that had investigated the efficacy of infliximab in the induction of remission in Crohn's disease.[3] In that study, 108 patients (age range 26 to 46 years) with moderate to severe Crohn's disease resistant to conventional treatment were recruited from 18 centres in North America and Europe. They were randomised to receive a single two hour intravenous infusion of infliximab or placebo. Outcome measures were ''clinical remission'' defined as a Crohn's disease activity index (CDAI) less than 150 at four weeks after the infusion, and ''clinical response'' defined as a reduction of 70 points or more in the CDAI score at four weeks after the infusion. In a subgroup analysis of the same study, changes in Crohn's disease endoscopic index score (CDEIS) from baseline after four weeks in a 30 patient subset of the original cohort, who also underwent colonoscopy before the infusion and four weeks after infusion, were reported.[5]

After reviewing the available evidence, the authors of the systematic review concluded that a single intravenous infusion of infliximab may be effective for inducing remission in Crohn's disease. Based on their review, they recommended a dose of 5 mg/kg.

CRITICAL APPRAISAL

Dr B assessed the quality of the systematic review using the critical appraisal checklist published by the Critical Appraisal Skills Programme (CASP), Oxford, UK.[6] A summary of Dr B's appraisal is shown below:

Summary of the appraisal

Did the review address a clearly focused question?

The reviewers aimed to evaluate the efficacy of infliximab in the induction of remission of Crohn's disease and to determine adverse events associated with infliximab treatment in Crohn's disease.

Did the reviewers try to identify all relevant studies?

They searched MEDLINE, EMBASE, the Cochrane central register of controlled trials from the Cochrane Library, and the Cochrane Inflammatory Bowel Disease Review Group specialised trials register. They also hand searched articles cited in each publication obtained, and contacted leaders in the field and manufacturers of infliximab to try and obtain unpublished articles. The search strategy was not limited by language.

Did the reviewers assess the quality of all studies included?

The reviewers included one RCT on the effectiveness of infliximab in the induction of remission in Crohn's disease. The methodological quality of the trial was assessed independently by two reviewers using the criteria described in the *Cochrane Reviewers' Handbook*[7] and the Jadad scale.[8] Allocation of participants to intervention or placebo was random and allocation concealment was adjudged adequate. Investigators, all other study personnel, and patients were blinded to treatment assignments. Data were analysed according to the intention to treat principle. Although no subgroup analysis based on colonoscopic findings was prespecified by the authors of the primary study, they also subsequently reported results for a 30 patient subset of the original cohort, who also underwent colonoscopy before and four weeks after infusion.[5]

If the result of the study has been combined, was it reasonable to do so?

As only one RCT was found on the use of infliximab in CD, no meta-analysis was undertaken.

What are the main results and how precise are the main results?

As stated earlier, outcome measures of the primary study were ''clinical remission'' defined as a Crohn's disease activity index (CDAI) less than 150 at four weeks after the infusion, and ''clinical response'' defined as a reduction of 70 points or more in the CDAI score at four weeks. The authors of the systematic review reported their main results in relative risks (RR) and their 95% confidence intervals (CI). Four weeks after the infusion, 27 of 83 patients in the infliximab group *v* 1 of 25 patients in the placebo group were in remission (RR = 8.1 (95% CI, 1.2 to 56.9)). Fifty four of 83 patients in the infliximab group *v* 4 of 25 in the placebo achieved clinical response (RR = 4.1 (1.6 to 10.1)).

Dr B decided to also express the results on clinical remission (which he considered to be the most important outcome) in terms of absolute risk (AR) measures.[9] Based on data in the article, he calculated the AR of achieving clinical remission for patients receiving infliximab as 27/83 = 0.325 or 32.5%, and the AR of achieving remission for patients receiving placebo as 1/25 = 0.04 or 4%. Thus the absolute risk reduction (ARR) or risk difference with regard to the achievement of clinical remission is (0.325 – 0.040) or 0.285 = 28.5%. This means that in the study, receiving infliximab increased a patient's chance of going into remission by 28.5%. Dr B also felt that it would be necessary to express the results in a more user friendly way by calculating the number needed to treat (NNT) which, in this context, is defined as the number of patients who need to receive infliximab in order to achieve remission in one of them. The concept of NNTs has been discussed elsewhere.[9] Dr B calculated the NNT as the reciprocal of the ARR or risk difference, and this was 1/0.285 or 3.5. This means that in the population studied, about four people with Crohn's disease unresponsive to conventional treatment needed to receive infliximab in order to get one of them into remission.

Dr B was, however, aware that because the study was undertaken in a different population, he might not be able to extrapolate the calculated ARR or NNT directly to his own population, as these measures are dependent on baseline risk.[9] The calculated ARR or NNT apply only to populations whose baseline risk (the risk of going into remission without infliximab) is similar to the study population. He would be able calculate an ARR for his population using the relative risk figures if he knew the baseline risk of his population,[9] but no such local data on this were available.

In the subgroup analysis of patients who also underwent endoscopy, mean CDEIS in the infliximab group decreased significantly from (mean (SD)) 13.0 (7.1) to 5.3 (4.4) ($p<0.001$). No significant change in mean CDEIS was observed in the placebo group (changed from 8.4 (6.3) to 7.5 (5.4)). Changes in CDEIS showed a significant correlation with changes in the CDAI ($r = 0.56$, $p = 0.002$).

Were other important outcomes considered?

The review considered both efficacy and adverse events of treatment. The authors commented that the short term adverse effects observed with infliximab were, in most cases, not very different from those observed with placebo, but the sample sizes of the primary studies may not have been adequate to detect any increased risk in adverse events in patients receiving infliximab. The follow up period was also probably too short to allow adequate assessment of potential long term adverse events.

Despite the findings of the systematic review, Dr B was aware from his reading that adverse events reported for infliximab in case reports and case series included infusion reactions, infections, and headaches. Other members of the medical team also mentioned that there had been recent case series that have described a potential association between infliximab use and serious adverse events such as tuberculosis and lymphoma in adult patients.

Are the results of the systematic review applicable to my patient?

The primary study recruited patients from Europe and North America and the main inclusion criterion was active Crohn's disease unresponsive to conventional treatment. The age range of participants was 26 to 46 years. Dr B could not see any biological reason why a drug effective in a 26 year old with Crohn's disease would not be so in a 16 year old. The study had defined ''active disease'' as a CDAI between 220 and 400. In order to be certain that his patient satisfied this condition, he estimated a CDAI for her and it was 300, which was within the range. He was therefore satisfied that his patient could reasonably be considered to be fairly similar to the participants of the study. Because of the reports of infliximab triggering the development of tuberculosis, Dr B screened Laura for evidence of latent tuberculosis by performing a chest *x* ray and a Mantoux test, the results of which were unremarkable.

GETTING EVIDENCE INTO PRACTICE

Availability and cost

At this stage, based on Laura's condition, the clinical team's judgement and the available evidence, Dr B was convinced that Laura might benefit from infliximab. He was not sure whether the drug was available from the hospital's pharmacy. He approached the pharmacy department for advice. He was told they did not have it in stock but would order it if they got approval from the hospital's medicines management committee. A single dose of infliximab for his patient would cost about £1400 and, depending on her response, she might need further infusions in the future. The chairman of the committee was initially hesitant to approve the use of the medicine because of its cost and the possibility of other physicians demanding it once it was used on one patient. Dr B subsequently contacted him and provided him with more information about the patient's condition and the available evidence. The chairman was convinced about the weight of the evidence and gave his approval.

Patient preferences

Laura and her parents were approached and given full details about the drug and its potential side effects. They asked a number of pertinent questions, mainly on side effects and availability of other options. Laura in particular was keen to know whether this medicine would allow her to be discharged from hospital, to go back to school, and to go on holidays. They were not unduly worried about the reported side effects and were keen to try infliximab.

Outcome

She received a single dose of intravenous infliximab at a dose of 5 mg/kg. Within a week, her condition had improved dramatically and all her symptoms had begun to settle and her appetite had improved considerably. She was then discharged home. When she was reviewed in clinic three weeks later, she was extremely well and her symptoms had completely settled. No side effects had occurred. She also reported significant improvements in her quality of life as she was going out more, and in her own words ''doing what normal teenagers do''.

Evidence based policy

Following Laura's treatment the multidisciplinary team of consultants, junior doctors, nurses, and pharmacist had a meeting to decide on a policy for future infliximab usage. They agreed to task Dr B and another senior paediatric registrar to search the literature further, particularly for articles on children. Further searches identified no paediatric RCTs that had compared the effectiveness of infliximab with either placebo or another treatment. However, several paediatric case reports and case series were found which had suggested that infliximab might be effective in children and adolescents with Crohn's disease who are unresponsive to conventional treatment. One recent study of 21 children suggested that infliximab may be safe and effective as short term treatment of medically refractory moderate to severe Crohn's disease in a paediatric population.[4]

Based on the overall evidence from the medical literature, the team had extensive discussions with hospital managers, patient/parent groups, and pharmacists. Issues such as potential benefits versus potential harms, costs, patient preferences, and availability of alternatives were discussed. Following the discussions, an agreement was reached to consider treating patients with moderate to severe active Crohn's disease unresponsive to conventional treatment (enteral nutrition, mesalazine, steroids, and immunosuppressive agents) with a single two hour infusion of infliximab (5 mg/kg). Because of the potential risk of infliximab activating latent tuberculosis, the team agreed to screen patients for latent tuberculosis with a chest *x* ray and a Mantoux test before infliximab infusion.

A policy statement which included an assessment of the problem, a review of the evidence on infliximab, analysis of the evidence, and estimation of benefits and harms, assessment of patient preferences, and assessment of costs was written up. The team agreed to review the effectiveness of the policy continuously, and to update the policy in a year's time based on any changes in evidence, expected outcomes, alternative treatments, costs, or patient preferences.

DISCUSSION

Integrating available evidence, clinical expertise, and patient's preferences into the care of this patient was very useful and turned out to be beneficial for the patient. The clinical team were initially ''overfocused'' on the traditional treatments for Crohn's disease and did not consider the possibility of newer effective treatments until Dr B drew attention to the possibility of using infliximab. The acquired knowledge of evidence based practice equipped Dr B with the willingness and skill to search for evidence on this drug and having found it to apply it to the patient, taking into consideration her preferences and the availability and cost of the drug.

The practice of EBM involves a process of life long, self directed learning in which caring for patients creates the need for important information about clinical and other health care issues. Traditionally, the forum for training in critical appraisal has been the ''journal club'', but while such clubs have been shown to improve reading habits[3] and confidence in appraising the medical literature,[4] they may not improve the application of knowledge to clinical decision making or improve knowledge in a sustained fashion.[5] The traditional journal clubs may be unsuitable for teaching evidence based decision making because of their exclusive focus on critical appraisal. Furthermore, they usually present EBM as an abstract exercise rather than an integral part of the flow of patient care.[13] The traditional journal clubs of clinical teams should be adapted by incorporating the five step EBM model[1] including the formulation of answerable clinical questions, searching for evidence, critical appraisal, applicability of evidence, and evaluation of performance into the process of answering day to day clinical questions in order to make these skills more useful to everyday practice. The questions should reflect ''real world'' constraints faced by the busy clinician and should arise from actual patient care issues. The development and structure of such an EBM journal club has been discussed elsewhere.[13 14]

The practice and teaching of EBM should be part of the day to day care of patients. When they are built into our ward rounds, outpatient clinics, departmental clinical meetings, and so on, they can allow the whole clinical team to develop an evidence based approach to clinical decision making. Developing the ability to access information from the medical literature, critically appraising it, and applying it to patient care requires skills that need to be taught. Most practising paediatricians were not taught these skills in medical school. EBM training will provide child health professionals with the tools needed to overcome some of the common barriers they face when trying to use published reports to help solve patient problems.

Competing interests: none declared

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