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Mini Review

Discrepancies Between Real World Clinical Practice and Clinical Trials in IBD

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Abstract

Randomized, placebo controlled trials (RCTs) are considered to be the most appropriate study design to provide reliable evidence of efficacy and safety of different drugs used in therapeutic armamentarium for treatment of ulcerative colitis (UC) and Crohn's disease (CD). Despite that, gaps in knowledge and significant discrepancies still exist in how to use some drugs in clinical practice in comparison with results of RCTs and international guidelines. In this paper we would like to describe probably the most discussed issues including usage of azathioprine/6-mercaptopurine in clinical practice, new "biobetter" concept of subcutaneous infliximab CT-P13 and position of mesalazine in Crohn's disease patients.

Keywords: *Inflammatory Bowel Disease; Crohn´s Disease; Ulcerative Colitis; Mesalazine; Azathioprine*

Clinical trials versus real world - background

Drug controlled clinical trials have started to appear in clinical research since 1940's and are currently a gold standard in drug development and marketing. In theory, clinical trial is a planned experiment with aim to evaluate outcome of selected treatment or intervention for patients with a specific medical condition. Adequately designed and carried out trials provide the most rigorous method to provide reliable evidence of treatment efficacy and safety. There are several conditions and restrictions that should be fulfilled to enable reliable conclusions to be made. These include:

- Control group: An intervention must to be compared to any other intervention, in drug trials mostly placebo or other drug that has already been used.
- Randomization: Subjects are randomly allocated to treatment arms such that the allocation cannot be predicted in advance. This serves to achieve a fair comparison between treatments. Reliability of results depends on how well all biases have been avoided.
- Size: Since patients vary considerably in response to a particular intervention due to biological nature of the processes, sufficiently large numbers of participants are needed in order to obtain a precise estimate of any treatment effect.

Conducting a clinical trial is often a major commitment requiring substantial financial inputs. Large trials usually fall into two categories - commercially sponsored trials where funding comes from pharmaceutical company or public funded trials.

The first key step before designing a trial is to evaluate currently available knowledge in the field. This serves to properly define primary aim of the trial and to avoid asking questions that have already been answered. It also helps to minimize misleading interpretation of the results.

Essential document for the conduct of any clinical trial is a trial protocol, which provides details of the scientific design and practical organization of a trial. One of the important elements of the protocol is the definition of eligible participants, interventions, and outcome measures. Eligible patients are defined by a list of inclusion and exclusion criteria. If the overall eligibility criteria are too restrictive, it could limit the number of patients recruited to the trial. The trial would be too focused on a specific group of patients and generalizability of the results to the wider population would be very limited. However, if criteria are too broad, results might be too hard to interpret, and it could be unclear as to whom the results might be applicable. Another key design feature is a control group. Trials which have no control group provide very little information in addressing the main question which is efficacy of the treatment, since any effect of the treatment cannot be distinguished from an effect due to other reasons. Fair comparison of study and control treatments is achieved by randomization. That is essential process to avoid selection bias happening due to patients being allocated treatment according to some systematic arrangement or by the judgement of the investigator. The main reason why randomization is important is that any differences in outcome between the groups can be attributed to the treatment under investigation rather than other causes. This is achieved by helping the groups to be similar at baseline in terms of known and unknown factors. It also helps treatment groups, along with blinding, to be handled identically in all ways except treatment itself.

Knowledge of which treatment a patient is receiving can bias the results of a trial. In order to avoid such potential bias many trials, particularly drug therapy trials, are designed to be double blind where the patient, investigator and evaluator do not know which treatment a patient is receiving. If there is no standard treatment the patient may be given a placebo which is identical to the drug treatment under investigation except for the active component. Often the investigator and evaluator are the same person hence the term double blind. Trials where the patient only is kept unaware of treatment are known as single blind trials.

A successful clinical trial is one that provides reliable evidence of the efficacy and safety of a treatment and not one that necessarily produces a positive outcome in terms of a "statistically significant" result. There are two key design issues in clinical trials to enable reliable evidence to be attained - avoidance of bias and need to recruit a sufficient number of patients. The first of these issues is addressed by the use of randomisation, control groups and blinding (where appropriate). For the second issue an assessment needs to be made as to what constitutes a sufficient number of patients for the study. In particular there needs to be enough participants in the trial to give a good chance of detecting a clinically important treatment difference if such a difference exists while being able to reasonably conclude that no such difference exists if our results do not show it.

Main problem arising with clinical trials is the applicability of results to the general population of individuals with the same condition. It is unlikely that all patients with a specific condition would be eligible for a particular trial due to stringent inclusion and exclusion criteria of many clinical trials. For example, patients with specific phenotype or complications of Crohn's disease, such as active perianal disease, ileostomy or perforating behavior or patients that have already experienced specific therapeutic interventions or patients with selected comorbidities are usually not eligible. These patients are not considered suitable for most of drug clinical trials in IBD therefore large proportion of patients treated in real clinical practice is excluded. As a result of this, lower risk patients with better outcomes are often recruited into trials.

While well-designed trials ensure a fair comparison of treatments in the selected sample (internal validity), the results may not provide results relevant to what is happening in practice, i.e. the external validity is less good. Registry databases can provide important insight as to the applicability of trial results and also into the effect of intervention in the "real world" setting. These databases collect routine

data on patient characteristics, interventions and outcomes in many disease areas, hence are observational databases. The benefits these databases provide include assessment of how interventions are applied in practice and any changes in their application over time. Observational databases are also not restricted by limitations in the number of patients and so are more able to study rarer endpoints rather than rely on surrogate markers. Last but not least, the databases offer insight as to the rates of adverse outcomes associated with intervention in common practice. On the other hand, the main limitation of registry databases is that they cannot control for selection bias. Interventions are based on clinical judgement and not randomization. For example, many patients starting biological treatment according to the Czech Registry of IBD Patients on Biological Therapy (CREDIT) are in fact in clinical remission at baseline which is usually caused by treatment with large doses of corticosteroids prior to initiation of biologicals in order to alleviate acute symptoms in the patient. This interferes with straightforward evaluation of clinical efficacy after induction period.

There is much discussion over the role of clinical trials in relation to observational studies (study designs where individuals are observed and data collected but nothing is done to influence either the exposure or the course of events) for assessing the impact of exposures and interventions. There are many situations in which it is not possible or ethical to conduct a clinical trial. Further, they can also play a crucial role in developing hypotheses of the impact of some treatment which can be tested subsequently in a clinical trial. However, observational studies may be prone to considerable bias and this needs be recognised during results interpretation regarding the effectiveness of interventions. The potential biases that may exist in observational studies and their impact on the results need to be considered carefully, along with other possible explanation of results. For example, suppose that an observational study indicated an association between some exposure of interest and a disease. There are a number of questions that need to be answered before concluding that the association is real including whether the observed association could be due to bias, due to differences in the groups in the distribution of other variables such as age (confounding), or due to chance. Further if the observed results do reflect a real association it needs to be established whether the relationship is causal.

A well designed and properly conducted clinical trial is the most reliable method to evaluate treatments and interventions. Rigorous attention to these design issues and to the conduct of trials is required to ensure they produce reliable and robust results and that risk of any potential bias is reduced.

Azathioprine and 6-mercaptopurine in therapeutic armamentarium for IBD - is there a time for change?

Thiopurine analogues azathioprine (AZA) and 6-mercaptopurine (6-MP) are used in maintenance of steroid-free remission in inflammatory bowel diseases (IBD) - both ulcerative colitis (UC) and Crohn's disease (CD) - since 1970's. Efficacy of AZA for maintenance of remission in patients with CD seems to be modest (number needed to treat of 6) and it is well established when given in appropriate dose of 2 to 2.5 mg/kg/day and for sufficient time of at least 17 weeks [1]. In four placebo-controlled RCTs focused on maintenance treatment with AZA in patients with UC who were steroid-dependent or intolerant to 5-ASA it has been shown that in 232 patients followed for 1 year, the azathioprine therapy was superior (56% of patients) to placebo (35% of patients) for the maintenance of clinical remission [RR: 1.59; 95% CI: 1.19 - 2.11]. Unfortunately, no placebo-controlled data on endoscopic or histological remission, sustained clinical remission, or on serious adverse effects (SAEs) were available. In contrast to current clinical trials, different disease activity indices and endpoint definitions were used in the trials. That is one of the reasons for indirect comparisons with novel and potentially more potent agents being quite difficult [2]. The lack of efficacy of AZA and 6-MP could be related to delayed prescription at a disease stage when irreversible damage (symptomatic strictures or perforations) have already occurred. An alternative concept of "accelerated step-up care" using early intervention with immunomodulators was proposed by pediatricians more than 20 years ago. In a small randomized placebo-controlled trial conducted in 53 children with disease duration less than 8 weeks, combination therapy with corticosteroids for induction and 6-MP for maintenance significantly decreased the need for prednisone prescription and improved sustainability of remission [3]. The older population-based studies focused on effects of early use of azathioprine on the long-term results regarding surgery-free survival and brought inconsistent results [4,5]. Based on the results from RAPID and AZTEC clinical trials, the administration of azathioprine within

6 months or 8 weeks, respectively, from diagnosis of CD was no more effective than conventional management when evaluating duration of clinical remission [6,7]. The most relevant conclusion inferred from the RAPID study is that there is no need to start AZA at the time of diagnosis in patients with CD with high risk of disabling disease. This message is reinforced by the observation that in the conventional arm, approximately one-third of patients did not require AZA or biological therapy after 3 years, thus avoiding their short and long-term side effects. In the AZTEC study which included adults with Crohn's disease, early AZA therapy was not more effective than placebo in achieving sustained corticosteroids-free remission but was more effective in preventing moderate to severe relapse in a post-hoc analysis. Notably, a significant proportion of patients reported strong concerns regarding potential long-term adverse effects, despite continuing their maintenance treatment [8]. Concerns about prolonged treatments with thiopurines are stemming from data on potential risk of malignancies [9]. There is a major reason for international guidelines recommendations on the maximum duration of treatment with thiopurines in IBD to range between 3 and 5 years [10]. In Markov model which compared a risk-benefit of combined therapy of azathioprine with infliximab an increased risk of lymphoma, infection, and surgery did not outweigh the greater efficacy of combination therapy for those aged 35 - 65 years when considering therapy for up to 3 years. However, the risk of lymphoma may outweigh the benefits of the same combination therapy for those older than 65 years, particularly with long-term therapy [11]. In the further meta-analysis it was showed that thiopurine use of at least 1 year may increase the risk of lymphoma nearly 6-fold. However, the increased risk appears to revert back to the baseline after thiopurines discontinuation, suggesting that immunosuppression is the key factor associated with the increased incidence of lymphoma. The absolute risk is the highest for those older than 50 years. Young male patients (younger than 30 - 35) may also be a high-risk population. For patients of all ages and genders, the risk of lymphoma needs to be weighed against the potential benefits of therapy [12,13]. In current clinical practice, azathioprine and 6-mercaptopurine are still very frequently used in both CD and UC patients despite published results of randomised clinical trials and observational cohort studies that showed only modest benefit and frequent and potentially severe side effects. There remains an unanswered question whether thiopurines still belong to IBD therapeutic armamentarium in the third decade of 21st century, when more affordable drugs emerged and were introduced to clinical practice including biosimilar monoclonal antibodies, JAK inhibitors, and completely new biologicals (anti-IL-23 antibodies) or sphingosin-1-receptors modulators.

Do "biobetters" really exist?

In the last two decades, scientific advancements lead to development of highly effective biologics and small molecules targeting various inflammatory pathways. Regardless of the expanding therapeutic options, there is a proportion of patients who remain nonresponders or have breakthrough relapse. The existing therapies fail to achieve clinical response in almost one third of patients (primary nonresponse) and the subsequent response is lost in 40% patients during maintenance phase (secondary loss of response) [14]. Recently, a subcutaneous (SC) formulation of the infliximab (IFX) biosimilar CT-P13 has been approved for treatment of CD and UC, among other immune-mediated diseases. In a phase I study which compared IFX SC and IFX IV treatment in patients with active IBD, higher IFX trough levels were observed in the SC compared to IV maintenance group. An occurrence of neutralising anti-IFX antibodies at week 22 were numerically lower in the SC (6%) compared to the IV (15%) maintenance arm in this study [15]. Similar observations were made in rheumatoid arthritis patients in a phase I/III trial: 69.5% of patients were positive for neutralising anti-IFX ADAs in the SC group vs. 85.6% in the IV group [16]. Mechanisms potentially contributing to these observations are that higher IFX trough concentrations associated with SC compared to IFX IV may induce high-zone tolerance and decreased immunogenicity resulting in decreased formation of drug-antibody immune complexes [17]. The PANTS study demonstrated the development of anti-drug antibodies (ADA) against IFX IV in more than 60% of CD patients. This predicted low IFX concentrations, which in turn predicted treatment failure. Various factors have been suggested to influence the immunogenicity of infliximab including, among others, the genetic background of the patient, drug dosing and intervals, episodic versus scheduled treatment, drug trough levels or smoking [18]. It is possible that the mode of administration more so than infliximab itself influences this risk. The SC formulation of infliximab might provide potential benefits for patients in terms

of efficacy and tolerability after the failure of previous IV infliximab [19]. The concept of biobetters, or biosuperiors, a new category of biopharmaceuticals with better efficacy, longer half-lives, lower dosing frequency, or reduced risk of immunogenicity and side effects, has been guided by efforts to enhance treatment.

Treatment with aminosalicylates in Crohn´s disease - discrepancy between evidence and practice

Aminosalicylates (5-ASA) represent very effective therapy in patients with mild to moderate ulcerative colitis [2], but their role in the treatment of Crohn´s disease has been questionable. Although the first studies on 5-ASA - sulfasalazine in Crohn´s disease suggested its efficacy, later studies on 5-ASA failed to demonstrate any benefit over placebo or corticosteroids [20]. Two Cochrane reviews from 2016 concluded that high dose mesalazine was not superior to placebo neither for inducing clinical remission nor for maintenance of medically induced remission [21,22]. This evidence was also reflected in several national or international guidelines which did not recommend the use of 5-ASA in patients with Crohn´s disease [23,24]. Despite this fact, several population-based or database studies have reported frequent use of 5-ASA in patients with Crohn´s disease [25,26]. According to European inception population-based cohort 60% of Crohn´s disease patients received 5-ASA at least once during the initial 5-year follow-up [25]. Furthermore, 5-ASA are the most used drugs in elderly patients with Crohn´s disease with approximately 80% of elderly patients being cumulatively exposed to 5-ASA after 10 years since diagnosis in French EPIMAD cohort [27]. Furthermore, systematic review and meta-analysis of placebo controlled trials showed that 44% and 49% of patients with Crohn´s disease, respectively, were co-prescribed 5-ASA medications in induction and maintenance trials [28]. Of note, most of the induction trials (38 of 42) were trials of biological or immunosuppressive therapy including patients with moderate to severe Crohn´s disease. Although the authors observed a decline in 5-ASA prescription over time, still one third of patients (35%) in the trials were prescribed 5-ASA preparations [28]. The discrepancy between guidelines and clinical practice may arise from several reasons. According to qualitative survey on physician´s perception on 5-ASA use in Crohn´s disease, the main arguments for 5-ASA prescription were favourable safety profile, potential efficacy in mild colonic Crohn´s disease (based primarily on personal experience) and patient preference to avoid more potent immunomodulator treatment [29].

Conclusion

Interestingly, almost half of the physicians continued to prescribe 5-ASA despite their feeling the evidence does not support the use of 5-ASA in Crohn´s disease and the other half either doubted the results of the research or believed in their positive clinical experience in some subgroups of patients with Crohn´s disease [29].

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