ANNALS OF GASTROENTEROLOGY 2002, 15(3):263-270

Problems and challenges in the design of Irritable Bowel Syndrome clinical trials. Focusing on the future with the experience from the past

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SUMMARY

Irritable Bowel Syndrome (IBS) is a common chronic disorder that is associated with significant disability and health costs. Drug development for this disorder is complex for a variety of reasons. A review of the literature concludes that there are few studies, which offer convincing evidence of effectiveness in treating IBS symptoms. Future trials must be double blind, placebo controlled, use internationally approved diagnostic criteria and describe the randomisation method. Clear, well-defined outcome measures are necessary as well.

Key words: Irritable bowel syndrome, drug development diagnostic criteria, side effects

INTRODUCTION

Drug development for functional gastrointestinal disorders is more complex than development of drugs for infective, inflammatory or neoplastic diseases. There is a perceived need, however, for effective pharmacological therapies for patients with these disorders. Patients often feel that their symptoms persist despite the use of currently available therapies. Physicians feel that current drug therapies are inadequate and pharmaceutical companies see this therapeutic area as one of great financial potential.

Although a lot of clinical trials on irritable bowel syndrome (IBS) have been published, there is much uncertainty about how best to conduct them and wide disagreement regarding the various approaches to these investigations.

Compared with other trials, such as those of ulcer-healing drugs, with a clear disease entity, an obvious endpoint, and highly effective treatments, trials in irritable bowel syndrome (IBS) have many problems. The condition being treated is polymorphous, there are many possible endpoints, and most therapies have so far been only marginally better than placebo. Early trials were difficult to evaluate because of inadequate patient definition. Furthermore, most trials used patient preference ("which drug do you prefer?") or global scores of improvement ("better, unchanged, or worse). Finally, many trials recruited such small numbers of subjects that even quite large effects could have been missed. Klein highlighted these past inadequacies in a comprehensive critique in 1988,[1] that suqqested guidelines for IBS trials (Table 1). In a recent review[2] only 6 of the 45 included studies fulfilled all three criteria (Table 2) used to assess the quality of randomised controlled trials (RCT).[3]

In this review, we will focus on certain issues that affect the quality of IBS clinical drug trials and we will comment on future needs.

PATIENT DEFINITION

Early studies used diagnostic criteria for IBS that varied from study to study. Although variable bowel habit was usually required, this was not quantified. More importantly, pain was not always included in the definition, which was effectively one of exclusion criteria. In 1990 a working party produced the "Rome criteria",[4] which defined the syndrome more precisely. Studies planned since

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Table 1. «Klein Criteria» for Irritable Bowel Syndrome Trials[1]

1. Adequate patient definition
2. Specific measures of efficacy
3. Placebo control
4. Adequate length of the trial (³ 8 weeks)
5. Parallel group design
6. adequate baseline comparisons
7. Recording of side effects
8. Low dropouts (<15%)
9. Use of appropriate statistics

Table 2. Criteria used to assess the quality of RCT[3]

1. Adequate description of randomisation
2. Double blinding
3. Description of withdrawals and dropouts

then have generally incorporated either these rather restrictive "Rome criteria" or some variant of the published criteria as the basis of patient recruitment, so that patient groups in different studies should be more comparable and the studies more generalisable. However, only recently have we seen publications that have specified severity of complaints as an entry criterion.[5]

Atypical IBS

Another problem is that many patients, whom clinicians would regard as having typical IBS, do not meet the criteria. Patients whose symptoms are typical but do not quite meet the 25% rule on symptom frequency, or have pain and intermittent diarrhea but have no other features are excluded on strict "Rome criteria." Attempts have been made to simplify the inclusion criteria for abdominal pain or discomfort and diarrhoea and/or constipation. In a Swedish population this less restrictive definition agreed with both Rome and Manning criteria and matches clinical practice more closely.[6]

It is recommended that patients to be included in clinical trials meet clear standardised entry criteria. Limiting trials to defined subgroups of patients should be considered to enhance homogeneity of the study population.[2]

Source of patients

A related subsidiary question concerns the source of patients. In theory, responses may be different in patients recruited from primary, secondary, or tertiary health-care settings or in response to newspaper advertisements. The principle that should be applied is that patients should be recruited for trials from all sources to which an indication is intended. This means that trials of agents intended to achieve wide usage should deliberately recruit from primary, secondary, and tertiary healthcare (ideally in proportions that reflect the circumstances of clinical practice). Patients recruited in response to newspaper advertisements can be eccentric as trial subjects and should probably be enrolled only if an indication for this group of individuals is under consideration or if they can be shown to respond similarly to those recruited from primary healthcare. The effect of recruitment source on outcome responses can and should be evaluated by secondary multivariate analysis.[7]

Minimal symptoms

Any trial using a large proportion of mild cases would be considered to have studied the wrong patient group. Furthermore, one would predict that the placebo response would be high, and thus the numbers required for a significant result would be very large. However, the threshold for entry needs to be realistic. Previous studies using a daily computer-based symptom diary, which is probably the most accurate method of collecting symptoms, suggest that approximately 20% of otherwise typical patients will have only mild symptoms in the first 2 weeks of study and 33% of study days are in fact pain-free.[8] Interestingly, this same study showed that when it is impossible to add data after each particular day has passed, failure to record symptoms is common. The proportion of missing data increases with time, reaching 27% at 6 weeks. Thus, many apparently correctly completed diary cards are probably filled in retrospectively at a later date, a fact that needs to be taken into account when assessing the validity of such data. The length of time over which symptoms should be averaged to decide whether they meet entry criteria for minimal symptoms should probably be at least 2 weeks and possibly 4 weeks, to avoid excluding patients who have typical symptoms but have an atypical 1-2 weeks with minimal symptoms. Pain on 4 or more days per 2 weeks would seem to be a realistic criterion if one is not to exclude the majority of patients who present as outpatients.[9]

SPECIFIC ENDPOINTS

Because there are no objective markers of improvement of IBS, determination of efficacy in treatment trials is based on somewhat arbitrary scales. A change in abdominal pain, bowel habit and overall well being are the main outcome measures used in IBS trials, with bloat-

ing tending to be neglected.[2,10]

Abdominal pain is the cardinal symptom of IBS and should be used as the primary trial endpoint.[7] Until there is greater experience with how optimally to conduct IBS clinical trials, it seems essential to simplify assessments. Making reductions in stool frequency in patients with diarrhoea-predominant IBS and increases in patients with constipation-predominant IBS as the primary endpoints seem flawed. Changes in these symptoms can still be analysed as secondary endpoints and differences in the primary or secondary outcomes in patient subgroups (e.g., diarrhoea or constipation predominant) detected by secondary multivariate analysis.[7]

One approach that Klein strongly criticised was the use of a global assessment.[1] This criticism is not fully justified. Global assessments are problematic if patients have not been entered into a study according to precise diagnostic entry criteria. They may have limitations as the sole assessment if the agent under investigation is one that has a profound primary effect on mood, because a non-specific psychological improvement could be registered as a specific improvement in IBS. Provided these caveats do not apply, global assessment should appeal to those for whom making pain reduction the primary endpoint is too restrictive, because the multiple impact of IBS can be captured in a single measure. One possible example of this approach is illustrated by the development of the concept of "adequate relief" as an endpoint in clinical trials in IBS.[11,12]

Trials can be designed around titration of dose to treatment success[13] but this requires that the criteria for dose change are explicitly stated and tightly controlled. For clinical trials to be interpretable, the intervention and the endpoint must be conceptually completely separate. Otherwise the endpoint can become simply a measure of the intensity of the therapeutic rather than the disease activity. Such trials can only be interpreted if the final dose chosen is the primary trial endpoint.

PLACEBO RESPONSE

Placebo response in IBS RCT is extremely variable and high, most frequently between 40% and 70%.[14] Differences of this magnitude reflect not only the nature of the patients enrolled in trials but also the methods used to determine treatment response. It is impossible to be certain that even marked improvements are due to the intrinsic properties of the treatment being tested unless there is a placebo control group.

Another approach to placebo effect might be a lack of conviction that there is a large placebo response in the true sense of the expression in IBS. Several studies have shown that IBS is a cyclical condition characterised by periods of symptom activity alternating with relatively asymptomatic periods.[15,16] In general, these cycles seem to last 1-3 months. Some, but not all, studies have been able to relate symptom activity to the menstrual cycle in women. It seems likely that individuals may vary in their cycle rate, but this has not been specifically investigated. So-called placebo responses may equally well be temporary spontaneous improvements that are part of the condition.

How to reduce the placebo response

Several approaches to this problem have been tried.

Run-in period

Using a run-in period of 3 weeks either with or without placebo tablets and excluding those who improve may result in 40% of patients being excluded as placebo responders.[17] Even after this 3-week run-in period, those entered in an one study still showed a 55% response to placebo over the following 8 weeks. This suggests that the placebo effect continues to act over at least 11 weeks. Furthermore, with a condition in which symptom severity typically fluctuates, excluding someone who falls below a certain value is probably illogical. Those who improve over the first 2 weeks are likely to relapse subsequently, whereas those who deteriorate over this period are likely to improve owing to the tendency for regression to the mean. There is no clear evidence that this manoeuvre reduces placebo effect.[7,9]

Lengthening study period

When placebo response is plotted against the length of study, a parabolic curve is apparent, with placebo response maximum at around 6-8 weeks (Figure 1). Defining the true time course of this phenomenon would require more studies of 3-6 months duration, but there are few such studies in the literature. These trials suggest that the placebo response diminishes after approximately 12 weeks, allowing a clearly significant difference to be seen. Placebo effect was lost completely by 6 months.[18] The longest follow-up data came from trials of psychotherapy, where benefit is most obvious from 3-12 months, by which time placebo response is zero.[19]

On current evidence, as presented above, the ideal time of a low placebo response (<20%) may be achieved by running the trial for 3 months.[20] Such a trial may re-

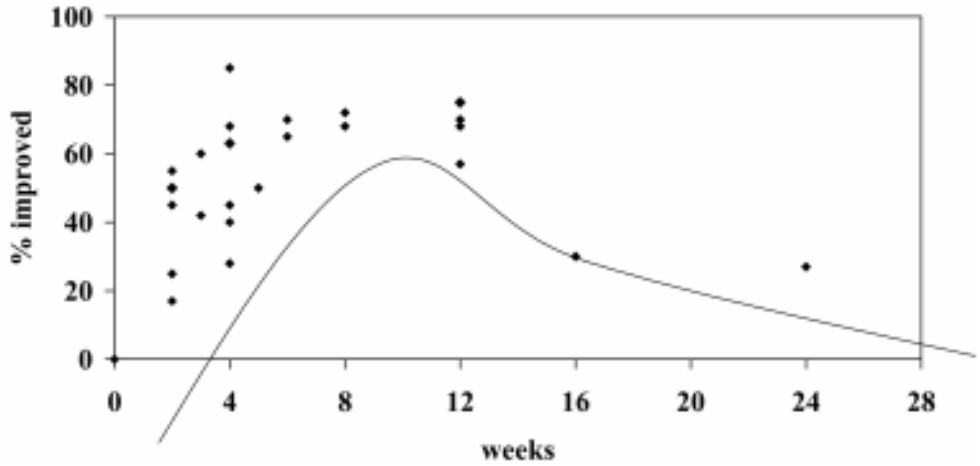

Figure 1. Placebo response plotted against length of trial for 27 randomised controlled trials with >30 patients performed from 1976-1998. There are not enough data points between 3-6 months, but it appears than the placebo response increases and then decreases with time, peaking at 8-12 weeks, which is currently the most common length of trial used.[9]

quire significantly fewer patients, but would it be easier to conduct? There is not much evidence on this point.

Lengthening the trial period may result in increasing the numbers of dropouts. Prior and Whorwell[21] reported dropouts by each visit and showed that these occurred steadily over 12 weeks with most being a result of lack of therapeutic effect of the trial drug. Similar findings are also reported by Kruis et al.[22]

Wherever this has been systematically reported, compliance also declined with study length[21] from 82% in the first month to 47% in the third and 40% in the fourth month. Prior and Whorwell[21] excluded 6% because of noncompliance over a 12-week study. Possibly the best way to measure therapeutic efficasy for any drug is the proportion of patients who choose to stay on the drug after the trial, suggesting a long-term benefit. Cann et al[23] reported that 18 of 28 patients continued to take loperamide, and 9 of them were still taking it at 1 year. Interestingly, in trials of food exclusion,[24] 80% of patients in whom some food intolerance was identified continued to avoid these specific foods; 20% no longer adhered to their diet.

ACTIVE COMPARATOR

This is relatively uncontroversial. Given that there are no highly effective treatments for IBS, there are few ethical problems with the use of placebos. It could be argued that smooth muscle relaxants are reasonably well established[25] and a smooth muscle relaxant could be an alternative comparator.

CLINICAL TRIAL DESIGN

The parallel group trial design for IBS RCT was used in 37 trials and the crossover design was used in 33 trials included in a recent review.[25] Klein[1] previously reserved particular criticism for crossover design. In fact, as with global outcome measures, it is the use of crossover designs under inappropriate circumstances that should be avoided.[26] Crossover designs reduce the numbers of patients needed to be recruited and are potentially more powerful, but are difficult to interpret if there is a big order effect. It is quite common to find a carry-over effect with, for example, laxatives, with which the improvement in constipation continues, for some time.[9]

A crossover design is inappropriate where there is a prolonged carry-over effect (whether this is mediated pharmacologically or by other mechanisms) or where there are circumstances in which substantial numbers of patients drop out before the crossing over study. In fact, studies employing a crossover design have resulted in apparently clean data, including studies in which antidepressants have been used and a carry-over effect would be anticipated.[27] If there is an order effect in crossover studies, it can easily be discounted by appropriate statistical analysis.

DOSE TITRATION

The idea of adjusting the dose according to the patient's response makes a great deal of sense because this allows one to take into account different body weight and drug metabolism. It also allows one to use the larg-

est dose tolerable, thus ensuring an optimal balance between therapeutic and associated but undesirable effects.[9]

Provided the reasons for increasing or decreasing the dose are clearly defined, variable dose regimens would seem to be sensible, mirroring as they do normal clinical behaviour. They would seem to maximise the chance of a good response and minimise the chance of missing a beneficial effect because the wrong starting dose was chosen. The alternative of using several fixed-dose regimens greatly increases the numbers of subjects required in the trial and seems unnecessarily extravagant.[9]

SIDE EFFECTS

It is important that these are systematically reported, both because side effects may limit subsequent use of the treatment outside a clinical trial[28] and also because they effectively unblind the trial, giving rise to the risk of bias in both patient and investigator.

DOCUMENTING RECRUITMENT AND DROP OUT

Keeping a record of the proportion of patients encountered in clinical practice considered suitable for recruitment and the number who dropped out has been done in very few studies, which are written as if this never occurred. This is essential, because most authors would like to believe that the results of their trial would be applicable to the entire population of patients seen with IBS. If, however, only a selected group of patients agree to enter, then this may not be true. Recording the proportion of approached patients who agree to enter is therefore very important and is part of the CONCORD recommendations for the uniform reporting of randomised controlled trials.[29] This should now be generally adopted, but so far full documentation has been reported in very few studies.

There are many possible reasons for nonparticipation, including factors not obviously disease related, such as inability to take time off from work or family commitments, difficulty with transport, inability to stop prohibited medication, and a desire to try other nonmedical therapies.[9]

Low dropout rates are equally important, because if a large proportion drop out, the remaining patients may be atypical and the results of the trial would not be generalisable to other settings. Most studies since the mid-1980s have reported low dropout rates,[9] but not all have given clear reasons for dropout. It is important to distinguish dropout from other causes, such as intercurrent illness, moving home, inability to take time from work, all unrelated to the specific study drug.

STATISTICS AND POWER

The use of appropriate statistics and the enrobment of enough subjects in order to ensure adequate power to answer the question under study definitively is accepted by all. Many studies in the literature used far too few patients to show an effect unless this was extremely large. A review of published studies of smooth muscle relaxants[30] reported the median number of patients studied to be 29 (range, 8-178) with a mean proportion of patients improving on the drug of 0.35 and on placebo of 0.08. The standardised difference of 0.68 indicates that 90 patients would be needed to give a power of 90% to detect such a difference with $p = 0.05$. Only one study included an adequate number of patients, suggesting either that at least some of the positive findings were a result of chance or else many negative studies were never published.

Most studies use an intention-to-treat analysis but very few are supported by a statistical power analysis and several outcome measures are frequently analysed without statistical adjustment.[25] Plainly adequate statistical planning should avoid such errors in the future.[9]

DESIGNS TO MEET SPECIFIC AIMS

The appropriate drug for different aims

A main criticism of IBS trials is that (varying) aims of treatment are usually not defined.

In the field of peptic ulcer, H_2 antagonists can be used to prevent or resolve single episodes of dyspepsia. Acid-suppressing drugs can also be used to bring to an end exacerbation of daily pain associated with active ulceration. Another use of acid-suppressing drugs is to prevent recurrence of ulcers and associated symptoms. Sometimes (e.g., use omeprazole to prevent nonsteroidal anti-inflammatory drug-associated disease) a heterogeneous group of patients is studied. The aim of treatment is to see whether natural history over the treatment period is altered. In the case of ulcer disease, with the understanding that *H. pylori* is a cause of many ulcers, a fifth type of study has been conducted. Patients can be enrolled at various stages in the ulcer cycle and reduction in ensuing dyspepsia, ulceration, and ulcer complications observed.

There are parallels for each of these scenarios with respect to IBS and, as with ulcer disease and dyspepsia, the same drugs may not be appropriate for each of them, and the trial design to evaluate them should vary. It is therefore worthwhile to consider what would be an appropriate drug and an optimal design for different aspects of IBS.[7]

Treatments taken as single doses to terminate an attack of pain

The drug to be used should have a short t_{max} and achieve maximum therapeutic effect after the first dose. Trials of treatment for this scenario might involve the issue of drugs to be taken at a later date when pain arises spontaneously.

In the trials of H_2 antagonists in acute dyspepsia, provocation using a dyspeptogenic meal was used. It might be possible to identify an analogous situation for IBS, such as entering a stressful situation or dietary provocation, for example, the consumption of a large amount of bran. Such a paradigm would also allow single doses of drugs to be tested for their ability to prevent an anticipated acute symptomatic event, as was the case in trials of dyspepsia. A crossover design would be appropriate. Whether treatment or prevention were tested, compliance would be a minor issue and patients would be inclined to tolerate side effects if they got acute relief. Simple measures of efficacy would be appropriate. A long term would obviously be inappropriate, and a crossover design with placebo comparisons would be better than a parallel group design.

Studies of this nature would answer the question frequently asked by patients, whether there are effective treatments that can be taken acutely to abort attacks at an early stage of symptomatology.[7]

Treatments over a brief period of time to speed up resolution of a period of exacerbation of IBS

Trials in these situations should be of short duration. Longer studies are likely to be confounded by an increasing incidence of spontaneous remission, and a drug that took a long time to act in such circumstances would not be therapeutically useful[7].

Treatments to take after termination of a period of activity to prevent relapse

In IBS, a rapidly acting agent affecting motility or sensation peripherally might be particularly useful, resolving acute symptoms while a centrally acting drug could work at a more fundamental level to prevent their subsequent recrudescence.

In dyspepsia and IBS, maintenance treatment can be satisfactorily assessed only if acute symtomatology has been resolved by acute treatment. For maintenance treatments, a greater use of more complex endpoints, including assessments of quality of life, becomes important. Maintenance trials need to be long, and there should be a facility for further prolongation beyond the primary endpoint assessment either on a formal blinded or an informal open-label basis.[7]

Discrete courses of treatment designed to achieve a pivotal change in the natural history of the condition

The analogy is *H. pylori* eradication treatment. Without knowing what the equivalent target is or indeed whether there is one, it is not yet realistic to contemplate such trials in IBS.[7] However, with growing understanding of the twin issues of visceral sensitivity and neuronal plasticity, this may become a realistic goal.[31]

CONCLUSIONS

The literature review of treatments for IBS identified few RCTs and poor overall quality of research. The majority of published trials failed to meet the criteria of acceptability. Several new drugs are currently being developed,[32] but there is a tremendous complexity affecting drug development in IBS.[28]

Animal models for functional disorders need to be developed that more accurately reflect the human condition.

The response in healthy volunteers in phase one studies may not parallel changes seen in patients. There have not been enough phase 1 and 2 studies establishing the physiological mechanism through which these drugs might be acting.

Recent phase 3 studies have involved large numbers of patients to achieve results in order to meet licensing requirements. Investigators in these trials often participate for financial reasons and lack the sense of "ownership" of the trial.[28] Phase 3 studies can be concentrated in a limited number of centres, each of which would be able to contribute a substantial number of patients. Investigators would then have a vested intellectual interest in ensuring a high quality study.

Improvements are needed to consider which patients are eligible for enrolment into such studies and consideration needs to be given to the psychological assessment

of patients entered into trials for functional disorders.[10]

In all trials of drugs in IBS there has been great difficulty in defining endpoints that reflect a beneficial effect on the patient's global well being, on IBS-related symptoms and specifically on pain, discomfort and bloating. While these issues require further exploration, the Rome 2 group has attempted to establish some endpoints that may be useful in clinical trials.[32]

A randomised, double blind, controlled, parallel group study appears the most robust. Minimising placebo response reduces the numbers needed to detect a significant difference. The optimum length of trial is probably >3 months, because the placebo effect takes approximately 12 weeks to start to recede. An adequate run-in period to exclude those with minimal symptoms seems sensible, provided the threshold is not set too high, since most patients experience moderate or severe pain only two to four times per fortnight. Dose titration should maximise the chance of detecting a benefit, and the change in dose can be used as an endpoint indicative of effectiveness.

There is much to be learned about optimal design of trials for IBS. Although it is a complex condition, progress will be limited if its assessment is not simplified.

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