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TUTORIAL

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Understanding clinical trials in migraine

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Abstract The following points are covered in this review. (1) How a randomised clinical trial in migraine is performed. The whole process from idea to publication of an article is reviewed. (2) How to understand a paper on clinical trials in migraine. The aim of the study, design of study, efficacy measures and presentation of results are reviewed. The aim of the study is often stated vaguely and it is suggested to look at the power calculations in order to understand the aim of the study. The aims and the results of the trial programmes of the triptans are reviewed. Results of the study should be presented with 95%CI. (3) How to understand meta-analyses in migraine. Relationship between meta-analyses and head-to-head comparative trials is reviewed; and it is concluded that head-to-head comparisons remain the "golden standard" with meta-analyses as a useful supplement.

Keywords Migraine · Randomized clinical trials · Meta-analyses · Head-to-head analyses

Introduction

Controlled randomised clinical trials (RCTs) are the basis for evidence-based medicine in migraine. Every clinician should therefore know how to understand and judge a clinical trial. A clinical trial is a long process that ends in the final study report and the publication of a paper in a peer-reviewed journal. There are many steps in this complicated process, and in order to understand the final product, the published article, some knowledge of the previous steps is desirable and useful.

This article will therefore try to help clinicians to understand how a clinical trial in migraine is or should be performed. Next, the article should be analysed critically and some points that can be used in such an analysis will be given. Finally, meta-analyses in migraine will be reviewed. For more general aspects on these points the reader is referred to References [1–9].

How a clinical trial in migraine is done

The most important steps in a RCT in migraine are summarised in Table 1. The general concept of a RCT in migraine is normally conceived by the pharmaceutical industry. As mentioned later in detail, the aim can be either to demonstrate that a drug is efficacious, that it is better than placebo, or better than a standard drug for some features, either efficacy or adverse events (AEs). The protocol is then written and depending on the aim of the RCT the number of subjects needed is calculated in the power calculations. Then suitable investigators are

Table 1. Most important steps in a clinical trial in migraine

Conception of the basic idea of the trial (most often by the pharmaceutical industry)
Protocol written and investigators recruited
Protocol approved by health authorities and ethical committees
Subjects recruited
Trial actually performed, and monitoring of trial
Trial data collected and trial analysed
Final report approved by senior investigator
Selection of authors (well recognised investigators)
First draft of paper written
Authors comments included
Final paper submitted to a journal
Referees' comments included
Publication of the paper

sought. In phase II RCTs and early phase III it will most often be headache specialists from headache clinics whereas in later phase III RCTs general neurologists and in some cases general practitioners may be recruited. The protocol is then approved by health authorities and ethical committees. In some cases ethical committees may object to the inclusion of placebo in comparative RCTs [10] but placebo is needed in order to test the reactivity of the sample [11]. Subjects are then recruited with inclusion and exclusion criteria either from the files of the investigator, from GPs or by general advertisement in newspapers. It is a general experience that the number of patients that fulfil the inclusion and exclusion criteria in one's files is less than expected ("the law of disappearing disease"). The trial is then performed. In acute RCTs there is most often one inclusion visit and one visit after the patients have treated an attack and filled in an attack report form. In some RCTs one tries to get the control visit within 7 days so that missing data can be filled in [12, 13]. During the prophylactic RCTs the patients keep a headache diary both during the run-in phase and during the treatment period. Control visits where headache dairies are collected are scheduled most often with an interval of 4 weeks. Throughout the RCTs the study is monitored by monitors collecting the case records and in some cases, especially in phase II RCTs, biochemical tests are done for safety reasons. The trial data are thus continuously collected and entered into a database, which is analysed as soon as the database is cleared. A detailed study report with demographics, results of the RCTs and safety data is then written up and then normally presented to a senior investigator who approves the report. A group of investigators (most often well recognised investigators), and in some cases also company employees, then form the publication committee for the RCT. Ideally the publication committee should be selected by all investigators before the start of the RCT, but this is very rarely done. One of the tasks of the publication committee is to decide on which journal to submit the final manuscript to (for impact of the journal, see later). In many cases the first draft of a manuscript is written by a professional medical writer based on the final study report. The authors who should have access to the final study report then comment on the manuscript, and their comments are then included. After some rounds of comments the final manuscript is submitted to the chosen journal. The decision of the editor is in many cases to publish on condition that some revision is done. This revision is then done by the publication committee, the paper resubmitted, and after some time, most often several months, the article is finally published.

It is estimated that the total time from the perception of an idea for a RCT to final publication is 3–5 years. The whole process is complicated and is in most cases funded and controlled by the pharmaceutical industry. There are, however, exceptions to this general rule, for example a RCT on riboflavin for migraine prophylaxis [14], which was conceived and funded independently.

Understanding a paper on drug trials in migraine

Aim and results of study

The aim of the first RCTs of a new drug, for example sumatriptan and topiramate, is to demonstrate that it is superior to placebo and define the dose-response curve [15–17]. All triptans were superior to placebo [18, 19]; and in most cases a dose-response curve was defined [20].

Furthermore, RCTs are performed comparing standard treatment with the new drug, for example ergotamine with sumatriptan [21] and propranolol with topiramate [22]. In a comparative RCT one can get a good impression of the aim of study by looking at the power calculations. This will show whether a difference or comparability is expected.

When a new triptan is compared to the standard triptan sumatriptan, the aim can be to demonstrate that:

- the new triptan is more effective for headache relief than the standard drug;
- the new triptan is equivalent to the standard drug with less AEs;
- the new triptan results in less AEs than the standard drug;
- the new triptan is better for freedom from pain after 2 h;
- the new triptan is better for sustained freedom from pain results;

- the new triptan has a quicker onset of action than the standard drug.

If one looks at the different triptan trial programmes, one can deduct the following about the aim of these programmes: AstraZeneca (zolmitriptan) went for *a better complete response* (a decrease of headache to none or mild and no recurrence). The complete response was, however, not different between zolmitriptan and sumatriptan and not different from placebo [23], most likely due to a high placebo response [11]. GlaxoWelcome (naratriptan) went for *less AEs and less recurrences*. The chosen 2.5 mg dose of naratriptan was chosen as a dose causing no more AEs than placebo [20]. This dose of naratriptan was inferior to sumatriptan, but higher doses of naratriptan were equivalent to sumatriptan [20]. In one RCT with recurrence-prone patients there were less recurrences after naratriptan than after sumatriptan [24]. Merck (rizatriptan) went for a *quicker onset of action*. In two RCTs rizatriptan had a quicker onset of action than sumatriptan [13, 14], whereas this was not the case in one RCT published much later [25]. Almirall (almotriptan) probably went for *superior efficacy* and *for less AEs*. In one comparative RCT [26] and in a meta-analysis [18, 19] 12.5 mg almotriptan caused no more AEs than placebo and less AEs than 100 mg sumatriptan. In the comparative RCT [26] and in the meta-analysis [18, 19] 12.5 mg almotriptan was comparable to 100 mg sumatriptan and apparently better for sustained freedom from pain in the meta-analysis [18, 19]; but in one large comparative RCT [27] 50 mg sumatriptan (25%) was superior to 12.5 mg almotriptan (18%) for freedom from pain after 2 h and also better for sustained freedom from pain [28]. Pfizer (eletriptan) went for *more efficacy*, and in one systematic review of 3 comparative RCTs 40 mg sumatriptan was superior to 100 mg sumatriptan [29]. Quintiles (frovatriptan), because of the 26-h half-life of frovatriptan [20], probably went for *less recurrences* and *less AEs*. In one comparative RTC the AEs were less after 2.5 mg frovatriptan than with 100 mg sumatriptan [30] (but the efficacy data including the recurrence rates from this RCT remain so far unpublished).

Johnson & Johnson (topiramate) went for comparability with propranolol and in one rather large RCT 100 mg topiramate was comparable with 160 mg propranolol [22].

Design of the study

A placebo control is needed in most cases. The subjective nature of the response measured in migraine trials, and the variable and sometimes high placebo response, up to 40% in acute treatment RCTs [13] and up to 47% in prophylactic RCTs [31], necessitate the use of the double-blind technique. To use a standard drug for comparison without placebo is similar to using historical controls, a method not to be recommended for controlled drug trials. If the stated aim of the study is to demonstrate that a new drug is better than a standard drug, then the standard drug will take the place of a placebo.

Either crossover or parallel group comparisons can be used in drug trials in migraine. Opinion is divided as to their relative merits and the practical consequences of the drawbacks (for example carryover effect, problems with blinding, etc.) of the crossover trial [11]. The main advantage of the crossover trial is its power, the probability of detecting a certain difference between treatments. In addition, with decreased variability in the crossover RCT compared with the group comparison, the probability of narrow 95% CI in comparative RCTs will increase. Furthermore, this design is often more powerful in detecting significant differences in AEs [32], and one can ask for the patient's preference with this design. The trend in acute treatment trials has been to use parallel group comparison [20], but this design demands inclusion of several hundred patients in each treatment group if comparability is to be demonstrated with narrow confidence limits. Approximately 500 subjects in each treatment arm were needed to demonstrate difference in speed of onset of headache relief [13]; even more if superiority on efficacy measures such as sustained pain free is to be demonstrated [33].

In prophylactic RCT the crossover design was previously used a lot [34], but in recent years large RCTs, including several hundreds of patients [16, 17, 22], have successfully used the parallel group design. The minimum effective dose (50 mg topiramate) and the optimum dose (100 mg topiramate) have been defined in these RCTs [16, 17, 22].

Efficacy measures

Acute treatment RCTs

Simple efficacy parameters such as the proportion of headaches resolved within 2 h of taking the drug [11] should be used. Only then can the clinician judge whether a clinically relevant effect has been observed. Another clinically relevant efficacy parameter is sustained freedom from pain [11, 18, 19]. In most migraine RCTs with triptans, headache relief, a decrease from severe or moderate headache to none or mild headache, has been used as the primary efficacy measure [18, 19, 35, 36]. This efficacy measure includes a decrease from moderate to mild headache, a decrease that is not clinically relevant for the patients [37].

Prophylactic RCTs
Migraine attack frequency should be used as the primary efficacy measure; indeed, most trials of active drugs have shown that efficacy is related to this parameter. The number of days the patient has migraine over a given time is also an acceptable efficacy measure and is simpler for the patients to record.

Treatment-limiting AEs are especially important in prophylactic trials [16, 17, 22], and in clinical practice, because many patients stop treatment because of them. So if the report on a prophylactic RCT indicates that active drug and placebo give rise to similar side effect incidences, the result should be treated with caution because it is probably attributable either to an inadequate AE reporting system or to the trial including too few patients [9].

Presentation of results
Preferably, the results of all the objectives stated in the study protocol should be presented in a subsequent publication [8]. The most fair and informative way of presenting the results is to give the confidence interval (CI), usually a 95% CI interval. When comparability of two active drugs is claimed, this should be evidenced by a narrow confidence interval.

The choice of journal is also important. The article can be published in a headache journal, a neurological journal or in a distinguished general medical journal. My impression of the impact of papers on sumatriptan is shown in Table 2. The sumatriptan articles published in *JAMA*, *NEJM* and *The Lancet* had most likely the greatest impact (+++++). One problem with papers published in these prestigious journals is that in some cases not all the objectives can be presented. In one whole issue of *European Neurology* there were only articles on sumatriptan and this had a considerable impact (++++) because this issue was suitable as a handout. Most of the other published papers had, in my opinion, only moderate impact (++ to +++).

Understanding meta-analyses

Within recent years several systematic reviews with meta-analyses of acute migraine treatment have been published [18, 19, 36, 48–54]. In addition, three systematic reviews of preventive migraine treatment have been published [48, 55–57]. One should distinguish between systematic reviews, where several RCTs of a single drug are evaluated by meta-analysis to get a more precise impression of its merits [49, 52, 53], and systematic reviews, where several drugs or administration forms of a drug are compared in a meta-analysis [19, 36, 48, 50, 52, 54].

In the systematic reviews of acute migraine treatment [18, 19, 36, 49–54, 58, 59], migraine was diagnosed according to the criteria of the IHS [60] and the same methodology was used [35]. Patients treated had moderate or severe headache and headache relief was defined as a decrease to none or mild [35], and this was the primary efficacy measure in most RCTs. Freedom from pain after 2 h, which is now the recommended primary efficacy measure of the Subcommittee of IHS on Clinical Trials [11], was also reported in most studies and was evaluated

Table 2 Published RCTs on sumatriptan in different kinds of medical journals together with the author's judgement of the impact on clinical practice (+ ,weak to +++++, big impact)

Publication	Sponsor	Impact on clinical practice (+ to +++++)
NEJM 1991 [38] subc suma	G	+++++
JAMA 1991 [39] subc suma	G	+++++
Eur Neurol [15] oral suma, Subc suma [40]	G	++++
Eur Neurol [41] oral suma *vs*. A+M	G	++
J Intern Med [42] subc suma	G	++
Arch Neurol [43] subc suma	G	++
Cephalalgia [44] subc suma	G	++
Cephalalgia [45] subc suma	G	++
Neurology [46] oral suma	G	++
Lancet 1995 [47] oral suma *vs*. A+M	S	+++++
From 1996 to 2003 mostly comparative RCTs with other triptans *vs.* oral suma [20]	V	++ to +++

G, Glaxo; *S*, Synthelabo; *V*, various sponsors (GlaxoWellcome, AstraZeneca, Merck, Almirall-Prodesfarma, Pfizer); *suma*, sumatriptan; *A*, aspirin; *M*, metoclopramide; *subc*, subcutaneous

in some meta-analyses [18, 19, 58, 59]. One of the meta-analyses [18, 19] also evaluated sustained freedom from pain, that is freedom from pain after 2 h, no use of rescue medication and no recurrence within 24 h, and consistency across attacks.

In addition, tolerability *vs.* placebo was evaluated in these systematic reviews.

The results of the meta-analysis of oral triptans [18, 19] for headache relief and freedom from pain within 2 h are shown in Fig. 1. Because the placebo response varies in different trial programmes the main emphasis when judging the results of the meta-analysis should be on therapeutic gains (percentage effect after active drug minus percentage effect after placebo [48]). From therapeutic gains it is evident that 2.5 mg frovatriptan is inferior to and 80 mg eletriptan superior to 100 mg sumatriptan for headache relief. For freedom from pain 10 mg rizatriptan and 80 mg eletriptan are superior to 100 mg sumatriptan. The results of the meta-analysis [18, 19] cannot stand alone and the triptans should be judged by a combination of results from the meta-analysis and the comparative RCTs with the triptans [48]. Such a combined evaluation of oral triptans is presented in Table 3. For details, see Ref. [48]. Results are generally the same in the meta-

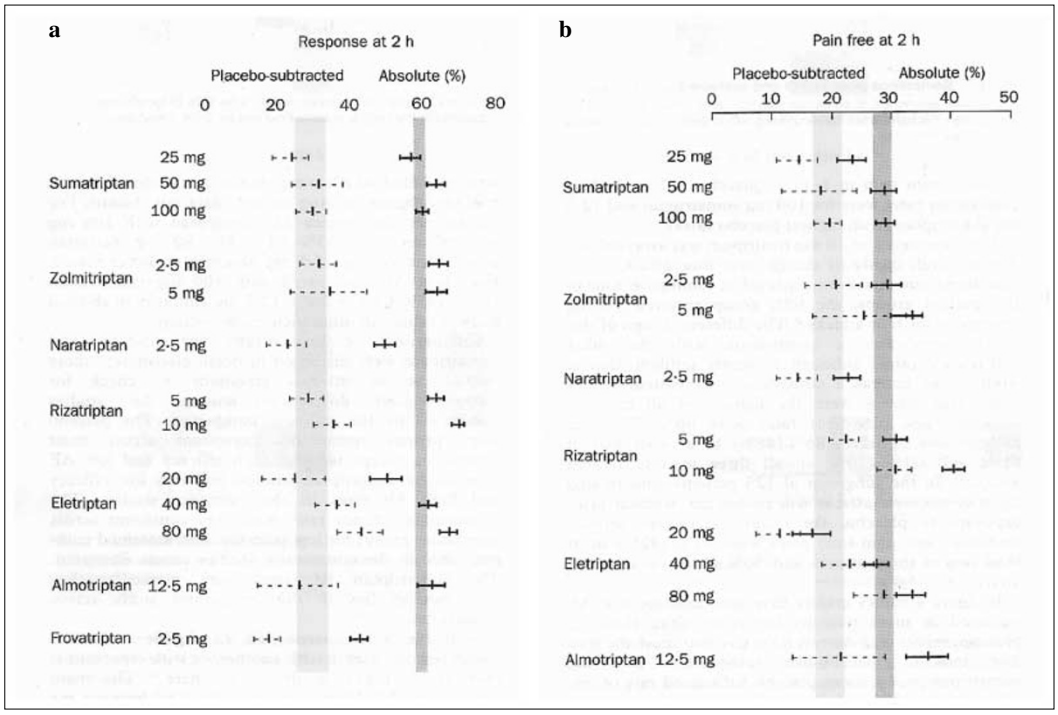

Fig. 1 Headache response (relief) (**a**) and relief from pain within 2 h (**b**) after seven triptans. The shaded area indicates the 95% confidence intervals for sumatriptan 100 mg both for absolute responses and placebo-subtracted results (from [18], with permission from the publisher)

Table 3 My personal comparison of the main efficacy and tolerability measures for selected oral triptans *vs.* 100 mg sumatriptan based on the results of the meta-analysis [18], direct comparative trials [19] and later published results [27, 33, 48], modified from [19]

	Initial 2 h relief	Sustained freedom from pain	Consistency	Tolerability
Sumatriptan 50 mg	=	=	?	=
Zolmitriptan 2.5 mg	=	=	?	=
Zolmitriptan 5 mg	=	=	?	=
Naratriptan	–	–	–	++
Rizatriptan 10 mg	=/+	+/=	++[a]	=
Eletriptan 40 mg	+	+/=	=	=
Eletriptan 80 mg	+	+	=	–
Almotriptan 12.5 mg	=	=	=	++

=, no difference when compared with 100 mg sumatriptan; +, better when compared with sumatriptan; –, inferior when compared with sumatriptan

[a]Consistency for rizatriptan 10 mg was investigated with a different methodology than normally used in the meta-analysis

analysis and in the comparative trials, with some exceptions: in the comparative RCTs 40 mg eletriptan is superior to 100 mg sumatriptan for headache relief and freedom from pain [29]; and 12.5 mg almotriptan is inferior to 50 mg sumatriptan for freedom from pain and sustained freedom from pain [27, 28].

When comparing drugs for the acute treatment of migraine, head-to-head comparative RCTs should remain the "gold standard". Comparative trials are, however, with a few exceptions [12, 33, 48], relatively small and may overlook differences. In theory, there may be a selection bias in head-to-head RCTs: patient responding well to the standard drug may be less likely to participate. In addition, not all drugs in a class of drugs will be compared in head-to-head RTCs [48].

Meta-analyses of drugs that underwent placebo-controlled RCTs with similar methodology can therefore be a useful supplement when drugs are compared. The main weakness of the meta-analytic approach is that there is no randomisation. In addition, the populations may not be totally comparable: there is possible bias in time with recruiting over many years, instructions to patients may vary and severity of headache (moderate/severe) may differ in different trial programmes. The problem with different severity of treated headaches is to some extent overcome by the use of therapeutic gain, as the placebo response also varies with the severity [61]. The main emphasis when judging meta-analytic results should therefore be on therapeutic gains and these results should be evaluated in context with the findings from head-to-head comparative trials.

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