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Review

Comparing vaccines: A systematic review of the use of the non-inferiority margin in vaccine trials

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ABSTRACT

Background: Non-inferiority (NI) randomized controlled trials (RCTs) aim to demonstrate that a new treatment is no worse than a comparator that has already shown its efficacy over placebo within a pre-specified margin. However, clear guidelines on how the NI margin should be determined are lacking for vaccine trials. A difference (seroprevalence/risk) of 10% or a geometric mean titre/concentration (GMT) ratio of 1.5 or 2.0 in antibody levels is implicitly recommended for vaccine trials. We aimed to explore which NI margins were used in vaccine RCTs and how they were determined.
Methods: A systematic search for NI vaccine RCTs yielded 177 eligible articles. Data were extracted from these articles using a standardized form and included general characteristics and characteristics specific for NI trials. Relations between the study characteristics and the NI margin used were explored.
Results: Among the 143 studies using an NI margin based on difference ($n = 136$ on immunogenicity, $n = 2$ on efficacy and $n = 5$ on safety), 66% used a margin of 10%, 23% used margins lower than 10% (range 1–7.5%) and 11% used margins larger than 10% (range 11.5–25%). Of the 103 studies using a NI margin based on the GMT ratio, 50% used a margin of 0.67/1.5 and 49% used 0.5/2.0. As observed, 85% of the studies did not discuss the method of margin determination; and 19% of the studies lacked a confidence interval or *p*-value for non-inferiority.
Conclusion: Most NI vaccine RCTs used an NI margin of 10% for difference or a GMT ratio of 1.5 or 2.0 without a clear rationale. Most articles presented enough information for the reader to make a judgement about the NI margin used and the conclusions. The reporting on the design, margins used and results of NI vaccine trials could be improved; more explicit guidelines may help to achieve this end.

1. Introduction

Different randomized controlled trial (RCT) designs can be used to evaluate the efficacy of a new drug or treatment. A superiority design aims to demonstrate that an experimental treatment is better than an already established treatment or placebo. A non-inferiority (NI) design aims to demonstrate that the experimental treatment is no worse than a comparator within a pre-specified margin [1–3]. NI designs are useful in situations where the efficacy of a new drug is deemed to be the same as the comparator but the new drug has additional benefits, such as less adverse events or reduced costs. NI designs can also be used to indirectly show the efficacy of a new drug over a placebo when the use of a placebo is unethical [3,4].

A new treatment is called non-inferior to the comparator if the difference between the comparator and the new treatment in an NI study is larger than the predefined margin (i.e. the boundary of the confidence interval exceeds the margin) [3]. The choice of the NI margin influences the outcome of the NI trial, although determination is complicated. Some general guidance for the determination of an NI margin is available. The size of the NI margin should be based on a combination of statistical and clinical considerations [4]. The U.S. Department of Health and Human Services, Food and Drug Administration (FDA) described a method to determine the NI margin. First, the total assumed effect of the active comparator over the placebo must be determined, and a conservative estimate of this effect should be taken to ensure that the test drug has an effect that is greater than zero. This conservative estimate is, for example, the lower limit of the confidence interval of the difference in effect when comparing the active control with the placebo. Second,

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a preserved fraction of the estimated effect should be determined, for instance 50%, demonstrating that the treatment is not unacceptably worse than its active comparator [2,3]. For example, an active comparator has a risk difference of 15% (95%CI 10–20%) compared with the placebo. The lower limit of the confidence interval (10%) is used as the conservative effect estimate and, using a preserved fraction of 50%, this results in an NI margin of 5%.

NI studies can also be used to study the efficacy, immunogenicity or safety of a *vaccine*. *Vaccine* trials are unique because most vaccines are highly effective and work to prevent disease. Using the method described above, high effectiveness with a small confidence interval would lead to a large margin. However, for preventive interventions, a small NI margin might be preferable: losing a large part of the effect on efficacy, immunogenicity or safety is undesirable. In addition, the studied endpoint in NI vaccine trials may be different from the endpoint in placebo-controlled vaccine trials. For example, in a placebo-controlled trial, a clinical endpoint, i.e. disease, is used. However, due to low incidence of this disease, this clinical endpoint cannot be used in the NI trial because of the required sample size; and antibody concentrations, expressed as the immune response rate or geometric mean antibody concentration or titre (GMC or GMT; referred to as GMT from now on), are then used as the endpoint. Obviously, if the endpoint of the placebo-controlled trial is different from the endpoint of the NI trial, the FDA method described above cannot be used. In previous Committee for Medicinal Products for Human Use (CHMP, part of EMA(European Medicines Agency)) documents, it was stated that '*In individual trials, delta can often be set to about 10 percentage point, but will need to be smaller for high seroprotection rates. Ultimately it should be based on clinical judgment and available evidence from previous clinical trials, and should be based on a case by case basis*' [5]. The defined definition of 'high seroprotection rates' is not discussed. Additionally, for infectious diseases, where herd immunity plays a role, this 10% might be a large difference. For the GMT ratio, suggestions on the preferable margin are less clear, and although either 1.5 or 2.0 is often mentioned, the inverse of these GMT ratios (0.67 or 0.5, respectively) is also used [3]. Despite these implicit recommendations, explicit NI margins for vaccine trials are not mentioned in the regulatory authorities' current guidelines [2,6]. Vaccines for different pathogens may also differ in, for example, their reactogenicity, the correlation between immunogenicity and vaccine efficacy and the variability of measurements, therefore, one explicit NI margin for vaccine trials may not be possible.

The CONSORT statement, published in 1996 and updated in 2006 and 2010, contains a checklist of recommendations for reporting RCTs. An extension of this statement, published in 2006 and updated in 2010, contains specific recommendations for NI and equivalence trials [7].

Because of the absence of clear guidelines for defining the NI margin to be used in vaccine trials, the aim of this review was to evaluate which NI margins were used in NI vaccine trials and how they were determined. In addition, we assessed whether the NI results were correctly interpreted. The influence of study characteristics, such as the aim of the study, the year of publication, the severity of the disease and the impact factor of the journal, on the choice of the NI margin was explored.

2. Methods

2.1. Systematic search and study selection

We performed a systematic search for NI vaccine trials in PubMed and the Cochrane Library on February 21st, 2013, in which the search terms used were related to non-inferiority and vaccines (Appendix 1). We excluded articles that were not written in Dutch or English, studies that were not performed on humans or in a trial setting, studies examining subjects other than infectious diseases, studies with a superiority design, abstracts from presentations and articles on bioequivalence studies. The study endpoints could include efficacy, immunogenicity and/or safety.

2.2. Data extraction

A standardized data extraction form was designed to obtain the required data from the articles. One person extracted the data from the articles and, in case of ambiguity, discussed the articles with another author. Any article where the reviewer believed that the conclusion was not in line with the presented results was also discussed with a second reviewer for confirmation. The data extracted from the articles were general characteristics, such as the author, year of publication, journal in which the article was published, infectious disease studied, study population, treatment arms, population in analysis (ITT or ATP) and measured endpoints. Characteristics specific for NI trials were also obtained, including whether the aim of the trial was efficacy, immunogenicity or safety, the NI margin, the way in which the NI margin was determined, the effect estimates and their relation to the NI margin, and the conclusion of the authors. Both NI margins on difference (efficacy, safety or immunogenicity) in outcome percentage and GMC/GMT ratio were extracted from the articles.

2.3. Data analysis

The frequencies of the characteristics of the included studies were calculated to describe the data. A relation between (the severity of) the disease and the aim of the study with the reported NI margin was analysed using a Chi Square or Fisher's Exact test. To categorize disease severity, the Dutch list of notifiable diseases was used [8]. Using Fisher's Exact test, we also analysed whether there was a difference in the explanation of the NI margin used in studies published before or after 2006 (the publication year of the extension on the CONSORT statement). The relation between impact factor of the journal the reviewed article was published in, and whether the conclusion could be (partially) checked or was inferred correctly was examined using the Kruskal–Wallis test. The NI margins of studies using the same treatment and comparator were also compared. Statistical analyses were performed using SPSS 19.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.).

3. Results

3.1. Study characteristics

In total, 494 articles from PubMed and 446 articles from the Cochrane Library were retrieved, with 380 duplicates, resulting in 560 articles eligible for screening using our inclusion and exclusion criteria. Of the articles, which were eligible for full-text analysis ($n = 260$), 177 were included in the analysis (Fig. 1).

The analysed articles were published between 1996 and 2012; however, most of the studies were published in the last 4 years (54.8%). Most of the trials were published in Vaccine ($n = 56$, 31.6%) or The Pediatric Infectious Disease Journal ($n = 37$, 20.9%). Most of the studies ($n = 153$, 86.4%) evaluated one treatment versus comparator(s). Most of the trials assessed whether combined or concomitant administration was as effective or as safe as separate administration of vaccines ($n = 69$, 39.0%), or a new vaccine was tested against an already available or licensed vaccine ($n = 57$, 32.2%; Table 1).