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Indirect Comparisons in Health Technologies Assessment

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This article is concerned with the methods of evaluating the effectiveness of new drugs, which would allow the doctor or the hospital head to make the right choice in favor of a particular medical technology. The author studies the general issues of indirect comparison of medical technologies in relation to a new method of evidence synthesis in decision-making process. Indirect comparison of the pegylated interferon to treat hepatitis C is an example of its use.

***Key words**: indirect treatment comparison, health technology assessment, hepatitis C, pegylated interferon.*

In clinical medicine, the doctors prescribe treatment for their patients on a daily basis, in particular - they appoint drugs (D). The matter is not to follow practical recommendations depending on the form of the disease, its severity, patient characteristics, etc.; but rather to choose between several treatments prescribed for the same patient population. For example, more than ten of angiotensin-converting enzyme inhibitors are currently available in the clinics, as they are considered the "gold standard" for arterial hypertension treatment. Which one is to choose for patients with a newly diagnosed disease, or in the presence of comorbidity, or for a patient older than 70 years? Similar questions arise for taxpayers, when one wants to make a decision on the financing of a particular medical technology. The use of clinical and economic analysis is considered to be a scientific approach to the adoption of such solutions, which implies comparing two or more medical technologies (eg, two drugs) in terms of their clinical efficacy and safety, and associated with linking financial costs.

Since the results of clinical and economic analyzes are gaining more and more weight in the evaluation of medical technologies (decision-making on the inclusion of particular drug into

restrictive lists, or on introduction of new technologies, etc.), the relevance of comparative studies of the effectiveness of drugs is now rapidly increasing. High-quality randomized controlled trials (RCTs) are recognized as a source of reliable evidence for evaluation of medical technologies, which is performed to obtain the most objective data for use, primarily in clinical medicine. At the same time different RCTs on the same drugs for the same patients may give different, sometimes conflicting, results both in terms of effect size and its orientation. The use of meta-analysis method allows to combine (synthesize, using statistical analysis) the results of several clinical trials, and thus to obtain an integrated assessment of the effectiveness of the drug. Despite this, often available meta-analyzes of RCTs are not sufficient enough to address both clinical and economic problems.

First of all, this is due to the fact that the vast majority of RCTs compares only two drugs, while usually drug choice is much wider for patients having particular nosology; then a comparison, which has not been in direct (head-to-head) clinical trials, may become the object of interest (Fig. 1, part 1). In addition, usually new drug is compared with placebo or standard therapy, whereas it is not often compared with a competing drug as often as necessary for practical reasons. This happens for obvious reasons: almost all clinical trials of drugs are sponsored by their manufacturers, who are not interested in comparisons with potentially competing product. Another problem is that the available RCT results can be obtained during the evaluation of medical technologies from patients that differ from the population of interest: for example, there is evidence of the comparative effectiveness of drugs in middle-aged people, whereas its use in the elderly is still of question.

The quality of available evidence still remains another important problem. As before, methodological quality of the clinical trials is the subject of debate, and the available results, unfortunately are not always sufficiently reliable. These same issues remain relevant when discussing the results of meta-analyzes. How reliable can be the results of these trials are included? How far do characteristics of their samples reconcile? Numerous differences in these parameters caused critics of meta-analysis techniques in general. Currently, in the absence of direct comparative clinical trials of drugs in practice there is often used a simple comparison of the absolute values of drug effects obtained in different trials. However, this approach is incorrect, as it deprives RCT of randomization - its main advantage. The result obtained through RCT is always relative (with respect to the control - placebo, standard therapy, etc.) and consists of specific (the effect of study treatment) and non-specific effects (placebo effect, Hawthorne effect, etc.).

If calculated difference was assumed to exist between the effects (a simple difference of the absolute effects) of matched drugs in a direct comparative study, too, it is also important to know

whether it is statistically important. The abovementioned approach does not allow to perform assessment. Technique of indirect comparison with respect to common control of drugs (adjusted indirect treatment comparison, ITC) can be used for evidence-based assessment of comparative effectiveness of the drug in the absence of direct comparative clinical trials [1]. Placebo or standard (basic) therapy may serve as a common control. Fig. 1 (part 2) presents the case when existing information shows the results of comparative interventions studies of A-B and B-C, while the researcher is interested in comparing the effects of A and B. It should be noted that the comparisons of A-C or B-C may represent the results of individual trials or meta-analysis of data (the synthesizing results of careful clinical trials). The scheme of indirect comparison is considered to be the simplest one. Using the technique of indirect comparisons, it is possible to analyze much more complex combinations of clinical trials [2].

The method of indirect comparison makes it possible to obtain reliable results, but only if methodological approach to its application is followed [3]. Samely as for meta-analysis, indirect comparison requires to use clinical studies of equal validity and generalizability. It is these issues that are the most difficult to manage at indirect comparison.

Key stages of indirect comparison:

I - Search for publications on research using pre-formulated search parameters;

II - Formation of studies population to be further analyzed, basing on inclusion and exclusion criteria;

III - Analysis of heterogeneity of studies / meta-analyzes included. At the same time it is determined if:

a) population correspond with each other on sex, age, severity and stage of disease, etc. (if they are not entirely consistent, it is discussed whether population differences can affect absolute or relative result),

b) doses and introduction of the drugs etc. are the same,

c) the same meta-model is used (in case of two meta-analyzes), ie whether models applied were of fixed or random effects, etc.

There are no strict criteria for determining the heterogeneity of the studies, so the debate on this topic continues [4];

IV –there should be defined relative effects dAC and dBC in direct studies of the A-C and B-C and C, respectively (point and interval estimates of effects); the effects odds ratio, relative risk, the difference between the values of continuous effects, the ratio of threats (in survival analysis) are usually studied;

V-calculation of the indirect relative effect dAB = dAC-dBC (point and interval estimates). It should be noted that randomization is not violated, because the relative effects of direct

comparisons are calculated before the synthesis of effects. Both probabilistic and Bayes approach may be used;

VI - a sensitivity analysis of the results in relation to studies included in the analysis, which are more weak methodologically;

VII - a description of indirect comparisons, which can be conducted in accordance with the recommendations of the National Institute for Health and Clinical improvement of the UK (National institute for health and clinical excellence, «Guide to the methods of technology appraisal», June 2008), sections 5.3.13-5.3.22 and also in accordance with [2, 4]. Therefore, even in the absence of direct comparative studies on methods of indirect drugs comparison, it possible to synthesize the necessary evidence, which have at least not less, and in some cases even greater, reliability [5]. At the same time there is likely to occur the situation when both direct and indirect comparison are presented. It is called a "mixed comparison" (English - mixed treatment comparison; Fig. 1-3). In this case, the results of indirect comparisons can be added to the meta-analysis and be used for testing the "stability" of the evidence, that only increases their reliability.

Illustration of indirect comparison effectiveness

Application of the method of indirect comparison is presented by comparison of pegylated interferons (PegIF), new drugs for treatment of chronic hepatitis C. Currently, there are produced two drugs of this group - PegIF-α2a (Pegasys, Hoffmann-LaRoche) and PegIF-α2b (PegIntron, Schering-Plough). Incidence and high cost of therapy of both drugs is the reason for research. For a long time there existed many different opinions on this issue, using cited data from two trials on comparison of these drugs, which was carried out by M.Rumi et al. and by A. Ascione et al, as main argument. [6, 7]. However these studies have several limitations, including the varied duration of treatment depending on the virus genotype: in patients with genotypes 1 and 4 – duration of treatment was 48 weeks, and for genotypes 2 and 3 it was 24 weeks; design of study was developed to detect a difference in the sampling of all patients, although the manual recommends the same duration of treatment regardless of virus genotype.

The results of a larger, qualitative IDEAL study gave final answer to the question given, although the method of indirect comparison could easily be applied for this situation [8]. We have studied two publications on RCTs that compared PegIF-α2b (M.Manns et al.) and PegIF-α2a (M.Fried et al.) with usual IF-α2b (Intron AR, Schering-Plough), which may be a common control with indirect comparison as well [9, 10]. Both studies have identical design and are open RCTs. Focusing on the date of publication of reports (2001 and 2002, respectively), we assumed that they were carried out at approximately the same time, which is important. Studies were

performed during 48 weeks of active treatment and 24 weeks of observation. In the trial, which was performed by M.Manns et al., there was applied PegIF-α2b at a dose of 1.5 mg / kg sc (n / k) once a week plus ribavirin at a dose of 800 mg / day, or IF-α2b 3 million units of n / a thrice weekly plus ribavirin at a dose of 1000 mg / day for weight <75 kg and 1200 mg for weight> 75 kg.

In both cases, the efficiency was assessed by frequency of sustained virologic response occurrence (SVR), whose criterion was lack of RNA of hepatitis C virus in the blood after the end of the observation period. Both studies were sufficiently powerful for assessing the effectiveness of this parameter. Data analysis was performed according to the assigned treatment (intention-to-treat). Therefore, the results looked equally reliable. Sampling studies were also identical. Both studies were carried out on the basis of several centers in several countries. They involved only adult patients who had not received previous treatment for their illness. Additional criteria for inclusion is presented in the Table. It is interesting that the sample sizes in the studies were similar: 511 and 505 patients in the experimental group, and 453 and 444, in the control groups in RCTs performed by M.Manns et al. and by M.Fried et al., respectively. What is more, the comparison showed similarity of characteristics. Then, data on the number of persons who had SVR was taken from the publications and used for calculation of relative risk (RR) of its occurrence, given 95% confidence interval (CI) for it.

In both cases, the likelihood of SVR in the group of PegIF was higher than in the the group of standard IF: in the study by M.Manns et al. RR = 1.15 (95% CI 1,02-1,30), and in the study M.Fried et al. RR = 1.28 (95% CI 1,20-1,46). We used these indicators for indirect comparison of drugs that showed no difference between the frequency of SVR: OR = 1.11 (95% CI 0,95-1,30). IDEAL, a previously mentioned study, showed a similar result: RR = 1.03 (95% CI 0,92-1,14). Therefore, point estimates, obtained through either indirect or direct comparisons of the effect, are very similar.

Moreover, the lower CI boundaries were practically the same. The lower upper limit in IDEAL study can be explained by twice-large size of the sample comparing with the studies used in the indirect comparison (approximately 2,000 and 1,000 patients, respectively). In this case, however, the point estimates of indirect and direct comparisons balance with each other’s CI, which indeed should be observed according to the principles of mathematical statistics. Therefore, the use of indirect methods of comparison with the correct methodological approach makes it possible to obtain reliable results that can be used in decision-making both in clinical medicine and in clinical and economic analysis.

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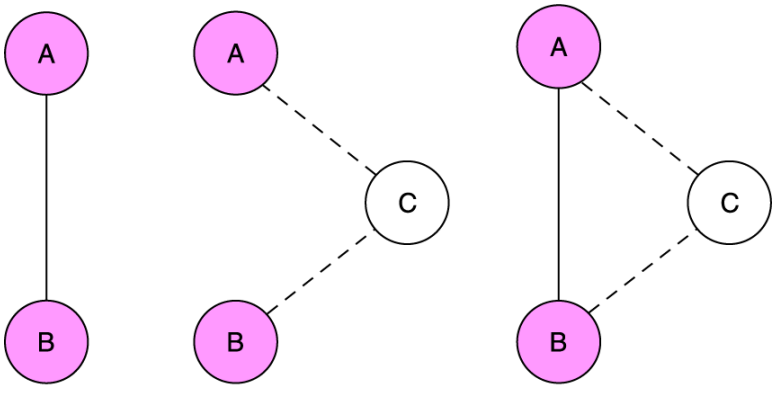
Table. Criteria for including patients into clinical trials of pegylated interferon

Inclusion criterion	**M. P. Manns et al., 2001**	**M. W. Fried et al., 2002**
Viral load	"+" RNA of hepatitis C acc.to	RNA of hepatitis C acc.to

	PCR	PCR > 2000
Diagnosis	Hepatitis C acc. to results of liver biopsy within 6 months before the study	Hepatitis C acc. to results of liver biopsy within 1 year before the study
ALT	Above the upper limit of norm	
Hemoglobin	>12 g for women and >13 g for men	
Neutrophils	>1500 ml3	
Platelets	>90•109/l	>100•109/l
Plasma creatinine	Not more than 1,5 norms	Within normal
Albumin and plasma bilirubin	–	Within normal
Extra criteria	Absence of other liver diseases Absence of HIV co-infection Absence of co-and / or decompensated somatic and mental disorders	



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