Oseltamivir (Tamiflu) shortens the duration of influenza-like illness by 13% (95% CI: 8% to 18%)

Harri Hemilä
Department of Public Health
University of Helsinki
Finland
http://www.mv.helsinki.fi/home/hemila
harri.hemila@helsinki.fi

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This is Feedback to the following Cochrane review:

Jefferson T, et al.:
Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children
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This Feedback is published within the above Cochrane review.
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This is an open access version of the Feedback.
This version has active links to all the references.

In studies measuring dichotomous outcomes, relative risk (RR) is a standard measure for comparing study groups. The purpose of using RR is to adjust for baseline variability in the occurrence of disease. It is easier to compare two trials on the basis of their RR estimates than on the basis of their absolute effects.

The relative effect should also be calculated for continuous outcomes. Although the duration of disease may vary randomly in placebo groups, there are also biological reasons why diseases in different placebo groups differ in their severity and duration. For example, in Analysis 1.1 of this review, the duration of influenza-like illness in the placebo group of trial WV15671 is 35% shorter than in the placebo group of trial WV15819/WV15876/WV15978 ($Z = 6.5$; $P = <0.00001$; 125h/192h). Such very large baseline differences are not explained by chance. Differences in the study populations, influenza seasons, study protocols, etc. are plausible explanations for the baseline variation. The above-mentioned baseline difference is much greater than any of those between the oseltamivir (Tamiflu) and placebo groups in the five trials of Analysis 1.1. As for dichotomous outcomes, the baseline variability of continuous outcomes can be adjusted for by calculating the effect in percentages, i.e., the relative effect. Furthermore, the percentage effect is informative for an average reader because the reader may form an opinion on whether, for example, a 10% or 20% average decrease in the duration is worth the cost and effort of the treatment. Separate from the absolute effect in days, the percentage effect shows whether the effect is small or large.

Therefore the effect of oseltamivir should be calculated also as a percentage effect. I calculated the relative effects for the five trials listed in Analysis 1.1, pooled them using the fixed effect inverse variance method of RevMan, and found that the average effect of oseltamivir is a 13% (95% CI: 8 to 18%) decrease in the duration of influenza-like illness.

Furthermore, the relative effect estimate makes it possible to compare the effects of treatments for related conditions. Influenza-like illness has substantial overlap with the common cold. In our Cochrane review on vitamin C and the common cold we calculated that ≥1 g/day of vitamin C shortens colds in adults by 8% (95% CI: 4 to 12%) and in children by 18% (95% CI: 9 to 27%) [1]. Another meta-analysis found that a high dose of zinc (>75 mg/day) as zinc acetate lozenges decreased the duration of colds by 42% (95% CI: 35 to 48%) and as zinc lozenges made with other salts by 20% (95% CI: 12 to 28%)[2]. The mechanism of the effect of vitamin C and zinc lozenges is not understood; however, there is no reason to assume that their effects are specific, for example, to the rhinovirus. If vitamin C and zinc lozenges have effects on diverse respiratory viruses, they might also have an effect on influenza viruses. In mice, influenza infection decreased vitamin C concentration in bronchoalveolar lavage fluid [3]. In mice, vitamin C deficiency

increased lung pathology caused by influenza infection [4]. An early study with influenza patients reported that the occurrence of pneumonia was 80% lower (2 vs. 10 cases) in the vitamin C group, suggesting that vitamin C might also have an effect on influenza in humans [5,6]. If the effects of vitamin C and zinc lozenges on influenza-like illness are of the same magnitude as their effects on the common cold, then the effects of these treatments compare reasonably with oseltamivir. The comparison of the percentage effects of oseltamivir, vitamin C and zinc lozenges may be useful when considering how future research resources concerning the treatment of respiratory virus infections might be allocated. In this respect, the type of effect measure has a much wider importance than just its use in evaluating the effectiveness of oseltamivir as an issue of its own.

Thus the relative effect estimate adjusts for baseline variations between trials, it is informative for most readers because people are familiar with percentages, and it makes it easier to compare different treatments for related conditions. For these reasons I would like to encourage the authors to calculate and report the relative effect estimates for oseltamivir in the next revision of the review.

References

[1] Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold.
Cochrane Database Syst Rev 2013:CD000980.
http://dx.doi.org/10.1002/14651858.CD000980.pub4
http://www.mv.helsinki.fi/home/hemila/CC

[2] Hemilä H. Zinc lozenges may shorten the duration of colds: a systematic review.
Open Respir Med J 2011;5:51-8.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969

[3] Buffinton GD, Christen S, Peterhans E, Stocker R. Oxidative stress in lungs
of mice infected with influenza A virus. Free Rad Res Commun 1992;16:99-110.
http://www.ncbi.nlm.nih.gov/pubmed/1321077
http://dx.doi.org/10.3109/10715769209049163

[4] Li W, Maeda N, Beck MA. Vitamin C deficiency increases the lung pathology
of influenza virus-infected gulo-/- mice. J Nutr 2006;136:2611-6.
http://www.ncbi.nlm.nih.gov/pubmed/16988135
http://jn.nutrition.org/content/136/10/2611

[5] Kimbarowski JA, Mokrow NJ. Colored precipitation reaction of the urine according
to Kimbarowski as an index of the effect of ascorbic acid during treatment of viral influenza
[in German]. Deutsche Gesundheitswesen 1967;22:2413-8.
http://www.ncbi.nlm.nih.gov/pubmed/5614915
Translation: http://www.mv.helsinki.fi/home/hemila/T4.pdf

[6] Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia.
Cochrane Database Syst Rev 2013:CD005532.
http://dx.doi.org/10.1002/14651858.CD005532.pub3
http://www.mv.helsinki.fi/home/hemila/CP