ACCEPTED ABSTRACTS

ABSTRACT 01) Safety of intravitreal injections: Non-inferiority of bevacizumab compared with ranibizumab.

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In Italy, the use of intravitreal bevacizumab has been endorsed in 2014 by the national medicines agency (AIFA) as an accepted off-label treatment for age-related macular degeneration (AMD). The studies that support the use of intravitreal bevacizumab have been reviewed quite recently by Moja et al. (Cochrane Database Syst Rev. 2014; CD011230) for AMD and by Virgili et al. (Cochrane Database Syst Rev. 2017; 6: CD007419) for diabetic macular edema (DME). Both of these meta-analyses provide sound evidence that intravitreal bevacizumab is effective and, as regards serious systemic adverse events (SSAEs), demonstrate that no difference exists between intravitreal bevacizumab and intravitreal ranibizumab. When equivalence or non-inferiority is investigated for two agents aimed at the same clinical indication, demonstrating the proof of no difference or noninferiority is a better level of evidence than demonstrating no proof of difference. Our purpose was to re-analyze the data on systemic safety published in these two meta-analyses by application of a non-inferiority design.
From the recent meta-analyses of Moja et al. and Virgili et al., we selected 9 trials for AMD (from page 54 of Moya et al.) and 3 trials for DME (from Appendix 8 of Virgili et al.). Our analysis was based on risk difference (RD), according to a standard random-effects model. The endpoint was the incidence of SSAEs. We planned a post-hoc analysis of one-sided 95% confidence interval for RD to determine the non-inferiority of bevacizumab vs. ranibizumab according to the afore-mentioned endpoint. Two separate analyses were carried out on AMD and DME. The outcome measure was expressed as RD.
In the case of AMD, bevacizumab in comparison with ranibizumab was non-inferior in SSAEs according to a 95% upper boundary at +4.5% (upper data set; p non-inferiority < 0.001). In the case of DME, bevacizumab again in comparison with ranibizumab was non-inferior in SSAEs, according to a 95% upper boundary at +3.4% (lower data set; pnon-inferiority < 0.05).
According to our results, we extended this finding by demonstrating that bevacizumab is non-inferior in safety compared with ranibizumab. Both post-hoc boundaries of our results were reasonable from a clinical point of view. We conclude that our results on safety, combined with those on effectiveness, can be useful to promote the use of intravitreal bevacizumab as opposed to intravitreal ranibizumab, mainly because the former costs less than the latter.

Abstract 02) Nephrotoxicity of three formulations of amphotericin B: a trial-sequential analysis

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Lipid-emulsion amphotericin B might have a nephrotoxicity similar to liposomal amphotericin B and lower than conventional amphotericin B.
After a search of the published literature, a total of 10 randomized studies were identified, in which conventional amphotericin B and/or lipid-emulsion amphotericin B and/or liposomal amphotericin B were compared with one another. The end-point was nephrotoxicity. The comparisons between these three formulations were carried out using trial sequential analysis (TSA).
Our results confirmed the lower nephrotoxicity of liposomal amphotericin B compared with that of conventional amphotericin B. In contrast, the lower nephrotoxicity of lipid emulsion amphotericin B did not meet the criteria of our TSA. In conclusion, according to our findings, liposomal amphotericin B should be the preferred option owing to its well-demonstrated reduction in nephrotoxicity. When nephrotoxicity is not an issue, conventional amphotericin remains the main alternative whereas the place in therapy of lipid-emulsion amphotericin B remains uncertain.

ABSTRACT 03) Area under the survival curve: a novel parameter to account for the presence of long-term survivors

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In the analysis of survival curves, medians are unable to capture the presence of a plateau in the final part of the curve. Evaluations of survival at "milestones" are already available to overcome this problem; however, since milestones require the choice of a fixed timepoint of follow-up, they lose the general validity which is the main strength of medians. We developed a new parameter based on the area under the survival curve (AUC) that accounts for the presence of a plateau.
The new parameter is defined as the ratio of AUC divided by median. The AUC is calculated by the trapezoidal rule. Medians are readily available for survival studies. In this preliminary analysis, we tested the new parameter using the same survival curves previously employed for proposing milestones.
In comparing progression-free survival between gefitinib vs paclitaxel+carboplatin in advanced pulmonary adenocarcinoma (1,217 patients), in the gefitinib arm the ratio AUC/median was 1.24 (AUC=11.3 months, median=9.1 months); in the controls, the ratio AUC/median was 1.27 (AUC=6.86 months, median=5.4 months). In comparing overall survival between ipilimumab+dacarbazine vs placebo+dacarbazine in advanced melanoma (60 patients), in the ipilimumab+dacarbazine arm, the ratio AUC/median was 2.06 (AUC=23.07 months, median=11.2 months;); in the controls, the ratio AUC/median was 1.77 (AUC=16.10 months, median=9.1 months). Unlike milestones, that have been proposed for the same purpose, the new parameter has a general validity and does not depend on the choice of a single timepoint in the follow-up.