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Antiviral prophylaxis for preventing herpes zoster in hematopoietic stem cell transplant recipients: A systematic review and meta-analysis

Hyun-Min Seo [a], Yoon Seob Kim [a], Chul Hwan Bang [a], Ji Hyun Lee [a], Jun Young Lee [a], Dong-Gun Lee [b], Young Min Park [a, *]

[a] Department of Dermatology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[b] Division of Infectious Diseases, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

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ABSTRACT

The optimal duration of prophylaxis for the varicella-zoster virus following hematopoietic stem cell transplantation (HSCT) remains unclear. The purpose of this study was to systematically review the available literature to determine the optimal duration of antiviral prophylaxis for preventing herpes zoster (HZ) in allogeneic and autologous HSCT recipients. The MEDLINE and EMBASE databases were searched to identify relevant studies. The relative risk (RR) of HZ was calculated using fixed effects or random effects models depending on heterogeneity across the included studies. We analyzed six observational studies comprising a total of 3420 patients. In all HSCT recipients, the overall incidence of HZ in the prophylaxis group and the control group was 7.8% and 25.6%, respectively, with a pooled RR of 0.31 (95% CI, 0.26–0.37). The incidence of HZ in the subgroup wherein prophylaxis was given for at least 1 year and in the subgroup wherein prophylaxis was given for less than 1 year was 2.1% and 15.4%, respectively, with a pooled RR of 0.23 (95% CI, 0.04–1.39). Taken together, our results demonstrate that antiviral prophylaxis can significantly reduce HZ in HSCT recipients, and suggests that long-term prophylaxis given for at least 1 year may be recommended for better preventive effects.

Contents

* Corresponding author. Department of Dermatology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul, 06591, Republic of Korea.
E-mail address: yymmpark6301@hotmail.com (Y.M. Park).

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1. Introduction

Herpes zoster (HZ) is caused by the varicella-zoster virus (VZV) and is a common complication following hematopoietic stem cell transplantation (HSCT), occurring in approximately 17–50% of allogeneic transplant recipients and 14–28% of autologous transplant recipients (Schuchter et al., 1989; Truong et al., 2014). According to a large retrospective cohort study, most cases of HZ occur during the first year following both types of HSCT, at a median duration of 6 months after allogeneic HSCT and 5 months after autologous HSCT (Erard et al., 2007). In addition to the risk of a more severe and prolonged local disease in this immune-compromised population, transplant patients are at risk for developing dissemination. Disseminated HZ can manifest as a cutaneous disease with erythematous papules, vesicles, pustules, or crusts appearing outside the primary dermatome, and with more severe systemic organ involvement, including encephalitis, pneumonia, hepatitis, and even death (Koc et al., 2000; Gnann, 2002).

The 2016 National Comprehensive Cancer Network (NCCN) Guidelines® in Oncology currently recommend prolonged antiviral prophylaxis in hematopoietic stem cell transplant patients for the prevention of HZ with a duration of at least 6–12 months following autologous HSCT, and with a duration of at least 12 months following allogeneic HSCT (Baden et al., 2016). However, there is a lack of evidence on the optimal duration of VZV prophylaxis. Moreover, following discontinuation of antiviral prophylaxis, there is always some concern about the possible disproportionate increase of HZ in patients. When this occurs (with this and other disorders), the phenomenon is often termed a “rebound” disease (Erard et al., 2007).

The aim of this study is to systematically evaluate the optimal duration of antiviral prophylaxis for preventing HZ in allogeneic and autologous HSCT recipients. Because our database search yielded only two randomized controlled trials with small numbers of patients (Boeckh et al., 2006; Klein et al., 2011), we included six observational studies for the meta-analysis herein. The analysis compares preventive effects between an antiviral prophylaxis group and a control group (i.e., no prophylaxis) on the development of HZ in HSCT recipients.

2. Methods

This systematic review was performed in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology Group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Stroup et al., 2000; Moher et al., 2009).

2.1. Data sources

Discrete literature searches were independently conducted by two reviewers (H.M. Seo and Y. S. Kim). The MEDLINE and EMBASE databases were searched from inception through May 1, 2016. Observational studies were identified using the following search terms: “herpes zoster” (Medical Subject Headings, MeSH) and “hematopoietic stem cell transplantation” (MeSH). All published articles written in English, limited to human studies, were included.

2.2. Data extraction and study selection

Two investigators (H. M. Seo and Y. S. Kim) independently reviewed the eligible reports in detail, and abstracted relevant information using a standard extraction sheet that covers study design, country, number and demographics of subjects, type of HSCT and antiviral prophylaxis, duration of antiviral prophylaxis, and duration of follow up. The investigators resolved any disagreement by consensus. Included for analysis were studies that evaluated the effectiveness of antiviral prophylaxis in HSCT recipients. Recipients of all ages were included, irrespective of VZV serologic status prior to HSCT (allogeneic or autologous). Recipients of solid organ transplants were excluded. Because there was heterogeneity in the duration of follow up across the studies, we gathered data for the longest period possible for analyses in each study.

2.3. Prophylaxis and outcome measures

Prophylaxis involved antiviral agents, including acyclovir, famciclovir, and valacyclovir. Because the majority of participants in the included studies received antiviral prophylaxis to prevent cytomegalovirus or the herpes simplex virus for durations of several days before transplant to about 1 month following HSCT, these antiviral prophylaxes were regarded as co-prophylaxis. We considered prophylaxis as the antiviral prophylaxis following co-prophylaxis. Comparisons were made between groups undergoing prophylaxis for the prevention of HZ and a control.

Primary outcome measures were the overall incidence of HZ between prophylaxis and control groups in all HSCT recipients. Secondary outcome measures were the incidence of HZ between prophylaxis and control groups in the recipients of each type of HSCT (allogeneic or autologous). The definition of HZ was as defined by the investigators of the included studies (Truong et al., 2014; Erard et al., 2007; Kanda et al., 2001; Asano-Mori et al., 2008; Kim et al., 2008a; Kawamura et al., 2015). Typically, this definition involved the presence of characteristic grouped vesicles on an erythematous base along a dermatome, a generalized cutaneous distribution, or microbiological and/or pathological confirmation.

2.4. Quality assessment

Two authors (H. M. Seo and C. H. Bang) independently evaluated the quality of the studies without blinding to authorship or to the journal of publication. The risk of bias in the observational studies included was assessed by the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS), which assesses the selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. All parameters were categorized as having a low, unclear, or high risk of bias (Kim et al., 2013). In the case of disagreement between the two investigators, consensus was reached after discussion.

2.5. Statistical analyses

We have presented dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs). Heterogeneity was assessed using χ^2 tests and I^2 statistics, with $p < 0.1$ for the χ^2 tests and with $I^2 > 50\%$ used as a threshold to indicate moderate heterogeneity. We pooled the data using a Mantel-Haenszel method to calculate a summary estimate of effect (Mantel and Haenszel, 1959). If moderate heterogeneity was seen, then the results of a random effects model were reported after exploring the causes of heterogeneity. Otherwise the results of the fixed effects model were reported.

All treatment regimens were combined for comparison, regardless of the kind or dosage of various antiviral agents. Subgroup analyses were conducted according to HSCT type and the duration of antiviral prophylaxis. The meta-analysis was performed with RevMan software, version 5.3 (Cochrane Collaboration, Copenhagen, Denmark).