Workshop Report

Cancer risk of immunosuppressants in manufacturing

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ABSTRACT

During the chemical and pharmaceutical production of active pharmaceutical substances which are intended for immunosuppressive therapy, the employees may be exposed to these substances via inhalation. Immunosuppressants are linked to development of certain types of cancers e.g., lymphoma or skin cancer in transplant patients. The development of these cancers in patients is linked to the level of immunosuppression needed for transplantation in order to avoid organ rejection. Below these levels, with the immune system functioning uninhibited, cancer is unlikely to develop.

An internal workshop was conducted to compare several pharmaceutical substances with the intrinsic property to cause immunosuppression, with the attempt to define the risk of healthy employees to develop cancer due to exposure to immunosuppressive substance at work and to determine the appropriate hazard classification for regulatory purposes. Data are discussed with emphasis on cyclosporine to reason the dose–response relationship and the safe level for occupational exposure. Our review indicates that if the exposure to cyclosporine at the workplace is below the threshold necessary to induce immunosuppression, the risk to develop cancer is negligible. Non-mutagenic immunosuppressants do not contribute to malignancies in occupational setting if their air concentrations do not exceed the immunosuppressive threshold limited with occupational exposure limits (OELs), which is for cyclosporine 17.5 μg/m³.

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1. Introduction

During manufacturing of active pharmaceutical substances, high technical and industrial hygiene standards have to be employed to avoid exposure of workers to intrinsic hazards, innate to these active ingredients. During the diverse production steps the employees may be potentially exposed via inhalation and skin contact.

There are two approaches to define the health hazard for employees during manufacturing; in the early stages of development of pharmaceutical substances, when human data are not yet available, the potential hazard has to be extrapolated from mechanism of action (MOA), toxicological and preclinical studies.

In later stages during clinical trials or when the substances have been used in patients for many years, patient safety data and the side effect profile is taken into account when determining the potential hazard of the substance. At this stage, a risk assessment is incorporated into calculation of OELs (Sargent and Kirk, 1988). It is important to appropriately extrapolate the adverse effects occurring in patients after oral or parenteral administration in order to define the relevant effects for employees, primarily exposed to substances by inhalation or transdermal absorption.

The effect of immunosuppression and the potential link to the occurrence of certain types of cancer (i.e., lymphoma and skin cancer) was first reported in the early 1970s in people with immunological disorders (Doll and Kinlen, 1970). Evidence was strengthened in the late 1980s when the same malignancies turned out to be one of the most common manifestations of HIV infection (Serraino et al., 2007). IARC has categorized immunosuppressants as human carcinogens (IARC, 1998). Moreover a recent IARC review confirmed that cyclosporine is considered to be a human carcinogen (IARC, 2012) due to several MOA such as increased oxi-
dative stress, effect on tumor suppressor factor β (TGFβ) (Hojo et al., 1999), effect on P-glycoprotein and immunosuppressive activity followed by virus-related cancers (IARC, 2012).

However occupational exposure was not mentioned in the IARC monograph. A two-day workshop was conducted to evaluate the available literature related to threshold and dose-response relationship of immunosuppressants. The purpose of this study was to determine the level of occupational cancer risk due to exposure to immunosuppressive substances and present the safe exposure level for cyclosporine at the workplace.

2. Risk assessment of immunosuppressants for employees during manufacturing

In early stages of development of pharmaceutical substances, Novartis applies a hazard based system, somewhat similar to the one described by Farris et al. (2006). Once the data is sufficient for calculation of OEL, this limit is used to determine the level of protection for the employees. OELs are the most important tools for exposure assessment and management at the workplace. OELs indicate the level of airborne exposure that the majority of working population can experience during an 8 h working day without adverse health effects (Sargent and Kirk, 1988).

Immunosuppressive substances which interfere with the DNA (e.g., azathioprine) are handled in manufacturing under the strictest conditions. For mutagenic substances, health based OEL cannot be determined based on health data, therefore the industrial hygiene monitoring data must show levels of exposure at the workplace below 1 μg/m³. The substances which are negative in in vitro and in vivo genotoxicity assays might still cause cancer, but they have a threshold which is used for determination of OEL. It is important to make a detailed assessment of all available studies (Naumann and Sargent, 1997). Based on results, the assessment of potential risk for humans is performed on a case-by-case basis. In addition the data from patients need to be carefully extrapolated for healthy adults.

In the literature the most abundant data related to immunosuppression and cancer development in humans can be found from the studies of transplant and cancer patients or patients with HIV. However no data was found related to risk of immunosuppression and cancer in healthy adults.

The primary route of exposure at the workplace is inhalation. In the absence of data for inhalatory bioavailability, 100% is assumed (Naumann and Weideman, 1995) (e.g., azathioprine, sirolimus, everolimus, mycophenolate mofetil and others). This may be an overestimation, however unless actual study results are available, the precautionary principle is followed.

The occupational health (OH) risk at the workplace is determined by the intrinsic hazard of the substance and the probability of manifestation of a particular hazard (Sargent and Kirk, 1988) depending on the exposure. Whenever the intrinsic hazard of the substance is high and the OEL is in the low μg/m³ range, accompanied by unknown or high bioavailability after inhalation, the OH risk is high. An OH risk and not the hazard alone then define the protection measures, which are required to prevent occupational illness.

Animal studies have shown that cyclosporine has relative bioavailability after inhalation in rats and dogs of 25% at 6 mg/kg/day, and of 6% at 2.5 mg/kg/day, respectively (unpublished study results). In human transplant recipients, the bioavailability of aerosolized cyclosporine was 8.2% (Corcoran, 2006) which is insufficient for its use in lung transplant patients.

The no-observed-adverse-effect-level (NOAEL) in the multiple dose oral toxicity study with cyclosporine in rats and dogs was 14 mg/kg/day with transient and reversible liver and kidney dysfunctions at 45 mg/kg/day. In an oral 13-week toxicity study in monkey, the NOAEL was determined to be 60 mg/kg/day. In the rat oral carcinogenicity study at doses up to 8 mg/kg/day, no increased malignancies were observed, and the NOAEL was 0.5 mg/kg/day. In a corresponding study in mice, however, an increased incidence of malignant lymphomas was observed in the highest dose of 16 mg/kg/day; no such malignancies occurred at the middle dose of 4 mg/kg/day (Donatsch, 1998). A study by Wassef et al. (1985) has shown that in rat oral administration of 5 and 10 mg/kg/day achieved serum levels, which were thought to be insufficient to secure adequate immunosuppression, indicating there is a threshold for this effect. The incidence of malignancies was shown to be dose-dependent. It has been shown in humans that repeated doses from 1–4 mg/day are required for effective therapy in psoriatic patients (Fry et al., 1988), which indicates a threshold level for this therapeutic indication. Any serum concentration below the threshold of pharmacological action would not cause immunosuppression. Based on presented results it can be concluded, that only profound and sustained immunosuppression after oral administration of cyclosporine leads to development of tumors, predominantly of the lymphatic system. Cyclosporine exposure limit has been calculated based on the lowest dose causing pharmacological/immunosuppressive effect of 175 mg/day, considering composite safety factors of 1000 using the calculation and safety factors proposed by Galer et al. (1992), Sargent and Kirk (1988), Naumann and Weideman (1995), Schwartz (1995), Naumann and Sargent (1997), Silverman et al. (1999) and IPCS (2001).

Immunosuppressants have a true dose-response relationship for their immunosuppressive effect, as shown by PK/PD data (Denton et al., 1999). A dose–response for cyclosporine was demonstrated by Burkart et al. (2003) in an in vivo study on transplant models in the mouse, and also in transplant patients, where it was shown that the low-dose regimen was associated with fewer malignant disorders but more frequent rejection (Dantai al., 1998). In studies by Corcoran (2006) and Iacono et al. (1997, 2006), aerosolized cyclosporine has demonstrated dose–dependent immunosuppression in animals and humans. For sirolimus the average dose to achieve target levels for immunosuppression in heart transplant pediatric patients was 0.25 mg/kg (Lobach et al., 2005). In a study by Harris et al. (1976) and Hammond-McKibben et al. (2001) it was shown that treatment with immunosuppressive drugs such as cyclosporine, sirolimus or fingolimod produce dose-dependent inhibition of allogeneic tumor rejection. Epidemiological data reveal that the length of exposure to immunosuppressive therapy and the intensity of therapy are clearly related to the post-transplant risk of malignancy (Gutierrez-Dalmau and Campistol, 2007).

Non-genotoxic immunosuppressants do not have direct carcinogenic effects. They switch off the immune surveillance and consequently lead to progression of either pre-cancerous states or viral infections causing cancer. It is generally accepted that increased risk of malignancies in patients is related to treatment regimen, length of exposure, level of immunosuppression (Vial, 2003). The overall burden of immunosuppression is more important than the agent itself (Gallagher et al., 2010).

Mutagenic immunosuppressive substances have a higher OH risk than those, which do not directly interact with the DNA. Cyclosporine should be considered as a substance with low risk to cause cancer at exposure below 17.5 μg/m³ considering negative mutagenicity and genotoxicity test results. Consequently based on the data presented, the carcinogenicity category 2 is assigned for classification and labeling purposes according to EU CLP (EC, 2008).

3. Conclusions

It has been presented with the case of cyclosporine, that immunosuppression works in a dose–response relationship with a clear
threshold effect. The risk of non-mutagenic immunosuppressants to cause cancer in an occupational setting is negligible if the air concentrations do not exceed the immunosuppressive threshold limited with OELs, which is for cyclosporine 17.5 μg/m³. The risk of the immunosuppressants to cause cancer at the workplace is should be defined on a case-by-case basis, considering all available data, taking a potential daily inhalatory exposure over a working life into consideration. For cyclosporine the carcinogenicity category 2 is proposed for classification and labeling purposes according to EU CLP.

Conflict of interest

All authors are employees of Novartis.

References


