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Guideline and Statement

Consensus statement for the diagnosis and treatment of drug-induced lung injuries ☆

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1. Definition and concept of drug-induced lung injury

Drug-induced lung injury (DLI) is defined as a lung injury that results from the specific use of a drug, including not only prescription drugs, but also over-the-counter drugs, herbal medicines, supplements, and illegal narcotics. In general, any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product is referred to as an adverse event (AE). AEs in which a causal relationship with a medicinal product is at least a reasonable possibility (i.e., the relationship cannot be ruled out), are referred to as adverse drug reactions (ADRs) [1]. In other words, an ADR is defined as all noxious and unintended responses to a medicinal product. A DLI is therefore an ADR that specifically occurs in the pulmonary system,

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which includes the lungs, bronchi, pulmonary vessels, and pleura.

2. Clinical disease types and their characteristics

No clinical disease types are specific to DLI. Similar to other respiratory diseases, DLIs are diagnosed on the basis of clinical examination, diagnostic imaging, and histological findings, and by their similarity to non-DLIs. Table 1 lists the main lesion sites, clinical disease types, and corresponding histological diagnoses of DLIs based on the non-DLIs or pathological conditions they resemble.

2.1. *Time of onset and course*

The length of the latent period between drug exposure and onset of DLI manifestations varies greatly, ranging from several minutes for hydrochlorothiazide-induced pulmonary edema to several years for amiodarone-induced interstitial pneumonia; however, the latent period generally ranges from a few weeks to months. The clinical presentations of DLI typically differ depending on whether the onset is acute or chronic. For example, acute DLIs develop in cases of non-cardiogenic pulmonary edema (NCPE), hypersensitivity pneumonia (HP), acute eosinophilic pneumonia (AEP), and diffuse alveolar damage (DAD), while chronic DLIs develop in cases of non-specific interstitial pneumonia (NSIP) or organizing pneumonia (OP).

2.2. *Response to treatment*

As described below, certain clinical presentations of DLI have a favorable clinical course, whereas others do not. Disease types such as eosinophilic pneumonia (EP), HP, and OP generally have a favorable clinical course and most patients resolve following drug discontinuation or treatment with adrenocortical steroids (corticosteroids). In contrast, DAD rarely responds to treatment and has a poor prognosis, and even if it resolves, fibrosis remains as a sequela. Chronic usual interstitial pneumonia (UIP) is also refractory to treatment.

2.3. *Risk factors*

Several risk and exacerbating factors for DLI have been identified. Non-specific risk factors include advanced age (60 years or older), existing pulmonary lesions (particularly for interstitial pneumonia), history of pulmonary surgery, decreased respiratory function, oxygen inhalation, radiation exposure to the lung, and existing renal impairment, which are all patient-related factors. Decreased renal function may also be a risk factor for DLI because it often results in elevated blood concentrations of the causative drug(s).

2.4. *Difficulties related to clinical disease types*

To describe DLIs based on their clinical disease form, the modifier "drug-induced" must be added to the disease term. However, depending on the causative drug, it can be difficult to differentiate between a DLI and the exacerbated form of an underlying disease. For example, gefitinib can induce acute exacerbation of idiopathic pulmonary fibrosis (IPF). Although "HP" is commonly used as a disease type of DLI, it also describes relatively acute drug-induced interstitial pneumonia in which an association with an allergic reaction is suspected, but it does not include interstitial lung disease that is clearly caused by inhalation of an organic antigen. Furthermore, the type of clinical disease is not specific to a particular drug; one drug may induce lung injuries characteristic of different types of clinical disease, and conversely, the same clinical disease can be induced by more than one drug.

3. Pathogenetic mechanisms

Most of the pathogenetic mechanisms by which drugs induce lung injury are unknown, although two basic mechanisms appear most likely. First, cytotoxic drugs may have direct toxic effects on alveolar type I epithelial cells, airway epithelial cells, or vascular endothelial cells. Second, the drug may activate immune cells by acting as a hapten or mimicking an antigen. These two mechanisms are likely modified by a variety of host and environmental factors, including genetic predisposition through the expression of drug metabolism- or immune-related genes, age, underlying pathological conditions in the lung, particularly pulmonary fibrosis or chronic inflammatory lung disease, and interactions with concomitant drugs.

4. Epidemiology

The incidence of DLI has not been accurately determined, but data reported in issues of the Pharmaceuticals and Medical Devices Safety Information indicates that reports of DLI have increased since 2000 (Fig. 1) [2,3], which corresponds to the year when gefitinib-induced lung injury attracted increasing attention to DLIs [4]. Gefitinib-induced lung injury later became a serious public concern in Japan. In actual clinical practice, causal relationships between drugs and DLIs are seldom recorded as "definite," but are typically recorded as "suspected" or "cannot be ruled out" (reports regarding marketed drugs often use such expressions, because most patients are receiving one or more concomitant drugs). All causative drugs, including suspected causative drugs and drugs for which a causal relationship cannot be ruled out, should be reported to the Pharmaceutical and Medical Devices Agency (PMDA, http://www.info.pmda.go.jp/) by the pharmaceutical companies, attending physicians, pharmacists, etc., that first identify them. The PMDA tabulates the data, which are then published in the Japanese Adverse Drug Event Report database (Table 2) on the PMDA website to ensure public safety [5].

Recently, evidence has emerged that the incidence of DLI in Japan is higher than that abroad [6]. Specifically, a high incidence of lung injury induced by the cancer drug gefitinib, which was first marketed in Japan in July 2002, has been observed, but gefitinib-induced lung injury has never become a public concern outside of Japan. The difference in incidence may be associated with differences in medical or health insurance systems, individual body constitution, drug dose, or availability of diagnostic tools, such as high resolution