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COMMITTEE REPORT

Criteria for safety evaluation of antimicrobial agents

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Principles and basic concepts on the safety evaluation of antimicrobial agents

The Japanese Society of Chemotherapy criteria for assessment of adverse reactions and abnormal laboratory values associated with antibacterial agents in study subjects [1, 2] (hereinafter referred to as "JSC's current criteria"), have been adopted in many clinical studies from immediately after their publication and are also cited in areas other than antimicrobial agents. Accumulated safety data based on the criteria have been submitted to the regulatory authorities in Japan for marketing approval applications. No inquiries such as uncertainty about the safety evaluations in clinical studies of antimicrobial agents have been made so far; therefore, the criteria seem to be recognized widely, including by the regulatory authorities.

However, there is a concern that the JSC's current criteria do not fit the present situation, because in recent new drug development the results of overseas clinical studies

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have been used aggressively or global studies have been conducted.

The Antimicrobial Agents Safety Evaluation Standards Committee of the JSC (hereinafter, the "Committee") has developed a concept of "abnormal changes in laboratory values" while taking into account management of the results of studies by overseas pharmaceutical companies. This concept was developed for the purpose of maintaining consistency with Western safety evaluation from a global viewpoint. With regard to adverse events in terms of symptoms and findings, we have summarized the information on adverse events in clinical studies of antimicrobial agents approved for marketing after 2005 (see Tables 6, 7) and discussed evaluation points for adverse events that occurred frequently in clinical studies of antimicrobial agents.

Abnormal changes in laboratory values

Previously, when assessing whether or not changes in laboratory values were adverse events, we classified them into two groups: a shift from a normal to an abnormal value or an aggravation from the abnormal value before administration. From the perspective of maintaining consistency with the evaluation of overseas clinical study data and in order to be concise, however, we have established an assessment procedure that enables each laboratory test item to be evaluated by a Grade based on standard values for these items. Furthermore, in consideration that the JSC's current criteria have been adopted in many clinical studies and results have accumulated, we fully analyzed the available data from clinical studies and avoided causing a large discrepancy from current evaluation results. In particular, the assessment results when defining abnormal changes as Grade 2 or higher according to the "Common Terminology Criteria for Adverse Events v 3.0 JCOG/JSCO version" [3] (hereinafter referred to as the "CTCAE"), which are generally found to be similar to the JSC's current criteria, the abnormal changes tended to be consistent with the assessment results based on the JSC's current criteria. We decided that the classification specified in the CTCAE could be used to promote the optimum safety evaluation of antimicrobial agents.

Details of the establishment of criteria for abnormal changes in laboratory values have been published in the interim report of the Japanese Society of Chemotherapy, Antimicrobial Agents Safety Evaluation Standards Committee [4].

Symptoms/findings

Events related to "gastrointestinal disorders" are the most frequent adverse events in clinical studies of antimicrobial agents, followed by "respiratory, thoracic and mediastinal disorders," "skin and subcutaneous tissue disorders," "general disorders and administration site conditions," "infections and infestations," "musculoskeletal and connective tissue disorders," and "nervous system disorders" (see Table 6). In order to individually define the severity of each adverse event, as is done with the CTCAE, the Committee assumed that a comprehensive analysis based on clinical findings and epidemiological data for each specialized field would be necessary and that ensuring universality would be difficult. Therefore, in our report we decided to show comprehensive criteria for the assessment of severity, regardless of the individual symptoms and findings. This concept was also based on the idea that the opinions of the physicians who actually take charge of clinical studies would be appropriate for the assessment of the severity of adverse events and their causal relationships.

Criteria for safety evaluation of laboratory values

Method for evaluation of abnormal changes and adverse events

Criteria for abnormal changes in laboratory values are shown in Table 1. Based on these criteria, when laboratory values are within the range of abnormal changes, accompanying any adverse symptoms or findings, or possibly resulting in them, or requiring additional tests or treatment, they should be handled as adverse events, and the causal relationship with the investigational drug should be assessed.

Laboratory values are known to fluctuate in relation to interindividual factors such as sex, age, and lifestyle, and intraindividual factors such as diurnal variation, type and timing of meals, physical exercise, body posture, and the sexual cycle. Therefore, whether or not changes in laboratory values are assessed as adverse events should be determined by distinguishing them as physiological changes or pathological (adverse) changes, while taking complete account of the background characteristics of the subject concerned, such as underlying disease and complications, and baseline values of the tests and/or changes unique to the subject if he/she underwent periodic laboratory tests before study participation.

Nonetheless, there may be cases where it is not appropriate to simply identify individual abnormal changes in laboratory values and determine them to be adverse events. Considering that abnormal changes in laboratory values involve the clinical background and adverse symptoms/findings in the subject concerned, it is more important to comprehensively evaluate adverse events occurring in the subject. In other words, when no diagnostic term can be defined for an adverse event, individual abnormal changes