

Literature Analysis of 53 Cases of Sindilizumab-Induced Adverse Drug Reactions

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Abstract: To examine the pattern of sindilizumab's adverse drug reactions (ADRs) and to offer a literature foundation for the medication's sensible therapeutic administration. The databases of the China Knowledge Network (CNKI), Wanfang, Wipu, PubMed, and Web of Science were searched for literature on Sindilizumab. The information on the timing, systems implicated, clinical symptoms, and reversal of adverse reactions was analyzed and summarized after the literature was compiled and its distribution examined. The 53 cases were spread throughout 51 literature papers, the first case report on Sindilizumab ADRs being published in 2020. The patients' ages ranged from 29 to 87, with a mean of 59.90 years. There were 38 men and 15 women among them. In all, 12 cases (22.2%) of the ensuing ADRs involved the endocrine system, which was then followed by the skin, digestive system, and neurological system. Sindilizumab should be monitored and followed up and documented during the course of drug administration, and ADRs should be detected and dealt with in a timely manner to avoid exacerbation.

Keywords: Sindilizumab; Adverse effects; Literature analysis; Safety; CRS

1. Introduction

A recombinant fully human immunoglobulin G (IgG4) type anti-programmed cell death receptor-1 (PD-1) monoclonal antibody called Sindilizumab binds to PD-1 and blocks PD-1 from binding to its ligands PD-L1 and PD-L2, alleviates immunosuppressive effects, activates T-cell function, and improves T-cell response to tumors immunosurveillance capacity and killing ability, generating a tumor immune response and thus acting as an anti-tumor agent^[1]. After receiving at least second-line systemic chemotherapy, the State Drug Administration approved the drug for marketing on December 14 (State Drug Quantifier S20180016) for relapsed or refractory classical Hodgkin's lymphoma. Subsequent approvals followed for advanced squamous non-small cell lung cancer, non-squamous non-small cell lung cancer, and unresectable or metastatic liver cancer, giving Chinese patients new hope. There have been case reports of negative reactions both domestically and internationally since its current launch. In order to give a reference for clinical use, the author has compiled and meticulously examined the ADRs of Sindilizumab both domestically and internationally.

2. Materials and methods

2.1 Source

In English, the keywords "Sintilimab", "adverse reaction", "induced", "case" side effect" were used, while in Chinese, "Sintilimab", "adverse reaction," etc. were used to search the databases of China Knowledge Network, Wanfang, and Vipshop. Keywords search Pubmed's Web of Sciences database was searched from its creation until the end of June 2022, excluding duplicate, poorly documented reports, and review-type literature. 51 eligible pieces of literature were found, along with 53 case reports and 33 pieces of Chinese literature.^[2-34], 18 articles in English^[35-52].

2.2 Criteria for evaluating the severity and relevance of ADRs

Refer to Common Toxicity Criteria Version 5.0 (CTCAE 5.0) of the National Cancer Institute

(CTCAE 5.0)^[53]: Grade 1: no need for treatment if asymptomatic or minimally unwell; Grade 2: moderate, requiring just local or minimally invasive care; Grade 3: serious or medically significant but not immediately life-threatening, necessitating hospitalization or prolonged hospitalization, and incapacitating; Grade 4: life-threatening, immediate medical care is required; Grade 5: death.

Association evaluation analysis using the internationally used Naranjo ADR assessment scale^[54], The evaluation criteria are: ≥ 9 as positive; 5-8 as very likely; 1-4 as probable; ≤ 0 as suspicious.

2.3 Methods

53 case reports were thoroughly read using the retrospective study method, and accurate data from the literature, including the patient's basic information, the original disease, the use of medications, adverse effects, the timing of ADR occurrence, the primary clinical manifestations of ADRs, regression, and management, was entered into Excel for classification and statistics.

2.3.1 Inclusion criteria

- ① Original clinical studies or case reports;
- ② Case reports published nationally and internationally;
- ③ Relatively complete information on the patient's basic profile, disease status, and medication such as Sindilizumab;
- ④ Cases with ADRs associated with Sindilizumab, meeting the criteria for ADRs^[55].

2.3.2 Exclusion criteria

- ① Clinical research literature, review literature and duplicate literature.
- ② Literature with unclear case descriptions.

3. Results

3.1 Patient age and gender profile

A search was made for 53 publicly available case reports of Sindilizumab, of which 38 cases (71.70%) were male and 15 cases (28.30%) were female. The cases ranged in age from 29 to 87, with a mean age of 59.90 years, and the majority (28 cases, 51.85%) were between 60 and 79 years old, as shown in Table 1.

Table 1: Age and gender of patients

Age/Years	Male/Example	Female/Example	Total/Example	Composition ratio %
20~39	4	4	8	15.09
40~59	10	4	14	26.42
60~79	23	5	28	52.83
≥ 80	1	2	3	5.66
Total	38	15	53	100

Note: 1) No patients under the age of 20 years were identified in this literature collection of cases, so they are not included in this count at this time. 2) One of the cases was reported as elderly and was not age specific, placed between 60 and 79 years of age.

3.2 Percentage distribution of pre-existing diseases

Following Hodgkin's lymphoma with three cases (5.66%), liver cancer with two cases (3.77%), gastric cancer with chordoma and thymoma, oesophageal cancer with chordoma, and colon cancer with two cases (3.77%), the majority of cases of Sindilizumab-related primary disease were lung cancer with 27 cases accounting for 50.94%, ovarian cancer, breast cancer, oral squamous cancer, malignant melanoma, oesophagogastric junction cancer, parotid cancer, ureteral cancer, gallbladder cancer and kidney cancer were all 1 case (1.89%), see Table 2.

Table 2: Percentage distribution of pre-existing diseases

Original disease	Number of cases/case	Composition ratio/%
Lung Cancer	27	50.94
Hodgkin's lymphoma	3	5.66
Liver cancer	2	3.77
Non-Hodgkin's lymphoma	2	3.77
Stomach Cancer	2	3.77
Chordoma	2	3.77
Thymoma	2	3.77
Esophageal cancer	2	3.77
Colon Cancer	2	3.77
Ovarian cancer	1	1.89
Breast cancer	1	1.89
Squamous carcinoma of the oral cavity	1	1.89
Malignant melanoma	1	1.89
Carcinoma of the esophagogastric junction	1	1.89
Parotid cancer	1	1.89
Ureteral cancer	1	1.89
Gallbladder cancer	1	1.89
Kidney cancer	1	1.89
Total	53	100

3.3 Time of onset, proportion of distribution and organs/systems involved in ADRs

Table 3: Distribution of ADRs by time of occurrence

Time/d	Number of cases/case	Composition ratio/%	Involved organs/systems
≤30	24	45.28	Skin (7) Digestive system (4) Cardiovascular system (3) Endocrine system (2) Respiratory system (2) Multi-organ organ (2) Hematological system (1) Immune system (1) Nervous system (1) Immune combined cardiovascular system (1)
31~90	14	26.42	Endocrine system (3) Multi-organ organ (2) Immune system (2) Haematological system (1) Skin and adnexa (1) Digestive system (1) Urinary system (1) Cardiovascular system (1) Immune system combined with cardiovascular system (1) Haematological system combined with respiratory system (1)
91~180	9	16.98	Endocrine system (5) Nervous system (1) Respiratory system (1) Hematological system (1) Skin and accessories (1)
181~360	4	7.55	Skin (2) Endocrine system (1) Respiratory system (1)
>360	2	3.77	Digestive system (1) Endocrine system (1)
Total	53	100	

The shortest time of ADRs was 1 h after dosing and the longest was more than 1 year after dosing, of which the majority occurred within 180 days after dosing (47 cases, accounting for 88.68%), of which the details are detailed in Table 3.

3.4 Involvement of organs/systems in ADRs and clinical presentation

ADRs caused by Sindiluzumab were most prevalent in the endocrine system (12 cases, 22.64%), whose common clinical disorders were autoimmune diabetes mellitus (5 cases, 41.67% of endocrine system damage), hypothyroidism (4 cases, 41.67% of endocrine system damage), and common skin and adnexal-related disorders (10 cases, 18.52%), according to a search of 53 published case reports of Sindiluzumab in China and abroad, the main manifestations of which were toxic epidermolysis bullosa

(4 cases, 40% of skin disorders) and cutaneous immune-related toxicity (2 cases, 20% of skin disorders); digestive system disorders (6 cases, 11.11%), the most common of which was immune-related liver injury (2 cases, 33.33% of digestive system disorders); In addition to this, ADRs involve multiple organs/systems such as multi-organ organs, cardiovascular system, respiratory system, haematological system, etc., as shown in Table 4.

Table 4: Clinical presentation of organs and systems involved in ADRs

Involved organs/systems	Main clinical manifestations of ADRs (cases)	Number of cases/case	Composition ratio/%
Endocrine system	Autoimmune diabetes mellitus (5) Hypothyroidism (4) Hyperaldosteronism (1) Hypopituitarism (1) Central dysuria (1)	12	22.64
Skin & Accessories	Toxic epidermolysis bullosa (4) Cutaneous immune-related toxicity (2) Purpura-like cutaneous vasculitis (1) Vitiligo (1) Dermatitis herpetiformis (1) Herpetiform aspergillosis (1)	10	18.87
Digestive system	Immune-associated liver injury (2) Immune-associated enteritis (1) Acute erosive haemorrhagic gastritis (1) Immune-associated pancreatitis (1) Immune-associated hepatitis (1)	6	11.32
Multi-organ organ	Abnormal thyroid function, immune-related enteritis, immune-related hepatitis (1) rash, abnormal thyroid function (1) hypothyroidism, diabetes mellitus, hypoadrenocorticism, haematotoxicity (1), myositis-myasthenia gravis combined with myocarditis (1), myositis-myasthenia gravis overlap syndrome combined with myasthenia crisis and myocarditis (1), cytokine release syndrome with multi-organ damage (1)	6	11.32
Respiratory system	Immune-associated pneumonia (2) Chest wall tuberculosis (1) Radiation-reviewed pneumonia (1) Tuberculous exudative pleurisy (1)	5	9.43
Cardiovascular system	Immune-associated myocarditis (4)	4	7.55
Nervous system	Immune-associated encephalitis (1) Immune-associated encephalopathy (1)	2	3.77
Blood system	Haemophagocytic syndrome (1) Thrombocytopenia (1) Leukopenia (1)	3	5.66
Immune system	Myasthenia gravis (1) Immune-related myositis with myasthenia gravis (1)	2	3.77
Cardiovascular system and immune system	Myocarditis combined with myasthenia gravis (1)	1	1.89
Immune system combined with respiratory system	CRS combined with pulmonary fibrosis (1)	1	1.89
Genitourinary system	Cystitis	1	1.89
Total		54	100

3.5 Handling and regression of ADRs

Among these 53 cases, except for endocrine system diseases such as thyroid function disease and diabetes mellitus, which were treated with symptomatic drugs, the rest of the immune-related diseases were treated with glucocorticoids, which is also in line with ICI-related toxicity treatment norms^[56,57].

4. Discussion

4.1 ADRs in relation to gender and age

A total of 53 patients were collected in this study, of whom 38 (71.70%) were male and 15 (28.30%) were female, with the number of males being half the number of females. Only three of the total number were applicable to Hodgkin's lymphoma, while the proportion applicable to lung cancer was as high as about 50%, and the majority of the 53 patients were aged between 40 and 79 years (42 cases in total, accounting for 79.24%). An analysis of the reasons for this may indicate that lung cancer, liver cancer, oesophageal cancer, and gastric cancer are related to their higher incidence in the elderly [58-61].

4.2 ADRs and clinical use of medication

The recommended dose of this drug is 200 mg/d-1 intravenously according to the instructions, of which only one case was 100 mg/d-1 (the dosage was not in accordance with the instructions; the exact reason is unknown).

4.3 Time of onset of ADRs

As can be seen from Table 3, the shortest time for ADRs with Sindilizumab to occur was 1 h after the first dose, and the longest could be more than 1 year. The time of occurrence of ADRs for most of the drugs was to be concentrated within 180 days after dosing, which was most common (48 cases in total, 88.9%), with one case of ADRs occurring >365 days.. The overall incidence of immune-related adverse reactions was 80%, and their toxicity could occur in any tissue or organ, with a median time of occurrence within 2 to 16 weeks after the start of treatment, 3 months, or even 1 year after the end of treatment. The median time of occurrence is 2 to 16 weeks after the start of treatment, or 3 months or even ≥ 1 year after the end of treatment, depending on the tissue and organ involved. Unlike conventional chemotherapy and targeted drugs, immune-related adverse reactions are a group of reactions based on immune damage that can affect almost all organs and tissues throughout the body, with a more insidious onset and a more diverse clinical presentation. Therefore, there is often uncertainty about the individual, timing, type, and clinical presentation of irAEs^[62].

4.4 Involvement of organs/systems in ADRs and clinical presentation

4.4.1 ADRs and endocrine system damage

In this analysis, endocrine system impairment was one of the most common ADRs for sindilizumab, with diabetes mellitus and hypothyroidism being the two most prevalent. The mechanism of diabetes mellitus due to ADRs is unclear and may be related to T cell regulation^[63]; The main clinical manifestations are dry mouth, weakness, excessive drinking, polyuria, and elevated blood glucose, and its treatment is mainly based on insulin hypoglycemia. Among the 12 cases of endocrine system diseases in this paper, 5 are autoimmune diabetes mellitus, and 2 of these 5 cases are type 1 diabetes mellitus with ketoacidosis and are admitted with high blood glucose^[63]In the cases of diabetes due to ADRs in this paper, the onset time was as short as 3 d and as long as almost 1 year, with an average onset time of around 12 weeks, which is approximately the same as the onset time due to the guidelines^[57].

In this literature analysis, the highest incidence of endocrine-related adverse reactions due to ICIs was hypothyroidism, followed by hyperaldosteronism and hypopituitarism. The mean event of thyroid function abnormalities occurred 10.4 weeks after the first treatment, which is consistent with the time of occurrence of the cases collected here. According to a meta-analysis, ICIs can cause hypothyroidism in between 5.5% and 7.8% of people^[64]. Additionally, some investigations have revealed that immune-induced thyroid abnormalities may also be related to cytotoxic T lymphocyte-mediated death of thyroid tissue, which may potentially be related to CTLA-4 gene polymorphism and autoimmune thyroid illness^[65].

4.4.2 ADRs and the skin and its accessories

In this literature analysis, one of the most common adverse reactions caused by ICIs of the skin and its adnexa was purpura-like dermal vasculitis, cutaneous immune-related toxicity, toxic epidermal necrolysis relaxation, herpetic dermatitis, and vitiligo.. The main adverse reactions include patchy papules with pruritus, purpura, blistering, a feverish rash with pruritus, severe bilateral lower limb

oedema with blistering, epidermal peeling, vesicular base flushing with oozing, etc. The main treatment modalities are hormones, immunoglobulins, and antibiotics, among which the more frequent case in this collection is toxic epidermolysis bullosa, the exact pathogenesis of which is unknown. It is a rare, acute, and critical case of necrolysis of the skin, which is severe and rapidly progressive, with a mortality rate of approximately 25%–35%^[66]. The onset of the disease can be as short as 3 days or as long as 330 days. Most of them appear within 1-2 weeks after the use of this drug, so closely observe the clinical symptoms of the patient, follow up on the observation, and ask for a dermatological consultation if necessary.

4.4.3 ADRs and the cardiovascular system

In this literature survey, there were a total of four cases of cardiac-related adverse reactions. The mechanism of immune-related myocarditis triggered by ICIs is still unclear, and immune-related cardiovascular adverse reactions have been reported among clinics, which are known adverse reactions in the instructions for Sintilizumab. The number of cases collected in this literature is relatively small, but in recent years, reports of ICIs-related cardiotoxicity have gradually increased, and its complications include cardiogenic. The incidence of ICI-associated myocarditis is likely to be overlooked, probably because the clinical symptoms of ICI-associated myocarditis are atypical, the diagnosis lacks a clear basis, and it is easily confused with other cardiovascular diseases^[67,68]. Our incidence of myocarditis due to ICIs is low at about 1.06%, but dual immune drugs have a higher mortality rate than single drugs (67% vs. 36%)^[68].

The main clinical manifestations of myocarditis in ICIs are chest tightness, shortness of breath, dyspnea, panic, and wheezing. Its treatment consists of glucocorticoids, immunoglobulins, and discontinuation of the drug with follow-up observation. The shortest onset time in these 4 patients was 7 days, and as many as 69 days; most of them appeared in 1-2 weeks. Therefore, when using this drug, patients should be asked about their past medical history, routine examination of cardiac ultrasound, ECG, and other auxiliary examinations, the need for differential diagnosis, close observation of patients' symptoms, strengthening follow-up, timely management, and consultation if necessary.

4.4.4 ADRs and multi-organ organs

Although the number of cases of multi-organ reactions caused by the use of Sintilizumab is small in this literature, it should not be ignored. The mechanism is still unclear and may be related to the excessive immune response caused by the systemic system.

4.4.5 ADRs and CRS

The package information for the medicine does not mention the adverse pharmacological reaction known as cytokine release syndrome. The symptoms of cytokine release syndrome include a high fever, chills, nausea, fatigue, muscle pain, capillary leakage, generalized oedema, flushing, hypotension, oliguria, tachycardia, dyspnea, liver failure, and renal impairment. Cytokine release syndrome is a severe systemic inflammatory response syndrome that is frequently brought on by the activation of immune cells and the release of large amounts of cytokines. Two instances of this adverse reaction were reported in this article, both occurring after two to three cycles of the drug Sintilizumab. The majority of these adverse reactions were infections.

5. Summary

Numerous body systems and organs are affected by ADRs brought on by Sintilizumab, and there is no shortage of dangerous and brand-new ADRs. Clinicians and pharmacists should pay close attention to ADRs related to Sintilizumab, and it is advised to identify patients' clinical symptoms and pertinent ancillary tests, strengthen follow-up investigation, suspend or stop drug therapy as needed, and actively treat symptoms while ensuring the safety of drug administration.

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