Lymphomatoid Papulosis and Tumour Necrosis Factor-α inhibitors: Infliximab, Etanercept and Adalimumab

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Summary

Infliximab, etanercept, and adalimumab are tumour necrosis factor (TNF)-α inhibitors, mainly used for pharmacological therapy of chronic inflammatory diseases. TNF-α inhibitors modulate the disease activity in an increasing number of chronic inflammatory diseases including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriasis, and psoriatic arthritis, as well as inflammatory bowel disease. Lymphomatoid Papulosis (LyP) is characterized by a chronic course of recurrent, self-healing papulonecrotic or nodular skin lesions. This condition has an indolent clinical behaviour and its malignant potential is uncertain. Statistical screening of VigiBase, the WHO global database of individual case safety reports, identified disproportionate reporting of the MedDRA Preferred Term (PT) "Lymphomatoid Papulosis" with adalimumab. A wider search was made to include other TNF-α inhibitors such as infliximab and etanercept. In the case series including adalimumab, infliximab and etanercept a consistent time to onset was identified, and there is biologic plausibility to support a signal. Communication of this signal is warranted because LyP could, in some high-risk patients, be considered as a previous disease strongly associated with other malignant lymphoproliferative disorders.

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Introduction

Infliximab, etanercept, and adalimumab are biologic drugs. Infliximab and adalimumab are monoclonal, anti-tumour necrosis factor (TNF)-α antibodies, and etanercept is a soluble protein p75 TNF-α receptor. Infliximab is a chimeric monoclonal antibody, composed of the variable region of a murine anti-human TNF-α antibody fused to the constant region of a human IgG1, whereas Adalimumab is a totally human recombinant IgG1 monoclonal antibody. Etanercept is a dimeric fusion protein composed of two soluble TNF receptor type 1 molecules linked to the Fc portion of an IgG1, which neutralises the soluble forms of both TNF-α and TNF-β, imitating the natural inhibitory effects.

Infliximab, etanercept and adalimumab were first marketed 20 years ago (infliximab-Remicade® in the United States of America (US) in 1998 and in the European Union (EU) in 1999, etanercept-Enbrel® in 2003 in the US and in 2000 in the EU, adalimumab-Humira® in 2002 in the US and in 2003 in the EU).

TNF-α inhibitors have had a remarkable effect on disease activity in an increasing number of chronic inflammatory diseases including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriasis, and psoriatic arthritis, as well as inflammatory bowel disease.

Lymphomatoid Papulosis (LyP) is characterized by a chronic course of recurrent, self-healing papulonecrotic or nodular skin lesions. The histological picture of LyP is extremely variable and may resemble different types of cutaneous T-cell lymphomas (CTCLs). The current World Health Organization (WHO) European Organization for Research and Treatment of Cancer (EORTC) classification has listed lymphomatoid papulosis as a primary cutaneous $CD30^+$ lymphoproliferative disorder.[1]

There are three main histopathological subtypes which have been identified. Type A, with a frequency >80% of cases, displays scattered small clusters of large $CD30^+$ cells mixed with a polymorphic inflammatory infiltrate; type B, (frequency <5%), is characterized by a mycosis fungoides-like infiltrate of small to medium $CD30^-$ atypical cells with cerebriform nuclei; type C, (frequency 10%), mimics a $CD30^+$ anaplastic large T-cell lymphoma.[2] There have been 3 additional types recently described, with a frequency <5%, such as type D that resembles primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma; type E characterized for being angiocentric and angiodestructive and, clinically, by large necrotic eschar-like lesions; and the last, and most recently identified subtype associated with the DUSP22-IRF4 gene region.[1]

LyP has an indolent clinical behaviour and their malignant potential is uncertain. The frequency of association between LyP and development of other malignant conditions such as lymphoma, $CD30^+$ anaplastic large-cell lymphoma, mycosis fungoides (MF) or Hodgkin disease, remains unclear in the literature. Some investigations suggest a frequency rate of 10% to 20%, while others suggest a cumulative risk up to 60 to 80% after a 20 to 30 years follow-up period. For this reason, long-term follow-up in patients with LyP is highly recommended.[2, 3]

Reports in VigiBase

As of January 2020, there were 15 reports for the MedDRA Preferred Term (PT) "Lymphomatoid papulosis" associated with adalimumab compared to about 3 expected cases based on the background of the database. Search was extended to other drugs in the same therapeutic class, identifying 11 observed cases with etanercept compared to about 3 expected cases and five observed cases with infliximab and about 1 expected; there were no reports with golimumab and certolizumab.

The 31 reports (adalimumab 15, etanercept 11, infliximab 5) were identify after the elimination of the potential duplicates by vigiMatch algorithm). These reports came from nine countries: the US (12 reports), the United Kingdom (5), Hungary (4), Spain, France, Germany, Greece (2 each), Austria and Canada (1 each). Nine cases were published in the scientific literature as case reports or observational follow up study.[4–10]

Eighteen patients were male, twelve were female and gender was not specified in one. The age was recorded for 25 patients, ranging from 16 to 82 years (mean 48). Therapeutic indication was recorded in 29 cases; for adalimumab the most frequent indication was Crohn's disease (7 reports), for etanercept

rheumatoid arthritis (4) and psoriasis (4), and for infliximab psoriasis (2 reports).

Most cases (19, 68%) were reported by physicians, followed by other health care professionals (8, 25.8%). In 14 patients the time to onset was given, with a mean of 739.5 days (just over two years), the median was 485 days (16 months) with a range of 24 days to 10 years. In 27 reports the event was considered as serious. The skin lesions were described as patches, plaques, or erythematous nodules in extremities and sometimes in the trunk.

Other malignant conditions were described in ten patients: anaplastic large-cell lymphoma T and null cell types in two (cases 4 and 16 in Table 1), cutaneous T-cell lymphoma in three (6, 25, 29), cutaneous T-cell lymphoma stage IV in one (28), T-cell lymphoma in one (13), lymphoma in one (2), large-cell anaplastic non-Hodgkin lymphoma in one (11) and squamous cell carcinoma of skin in one (8).

In 24 reports the TNF-α inhibitor was the only suspected drug, compared to ten reports in the case of adalimumab, five for infliximab and nine for etanercept. However, in two reports the pharmacological history included the use of another biological drug (case 1 and 2). The reference biologic drug (brand name) was reported as suspected in 22 cases, while the remaining cases were reported in International Common Denomination. No report was sent with biosimilar name, therefore, it is uncertain if any case was associated with biosimilar drugs. Regarding concomitant medicines, one report has at the same time, azathioprine and methotrexate as co-suspected drug, in four reports azathioprine, and in two methotrexate, were described as co-suspected drugs. In four reports azathioprine (two reports) and methotrexate (two reports) were classified as concomitant'.

The TNF-α inhibitors were withdrawn in 19 cases, however, only three patients were reported as recovered, three were recovering and two recovered with sequelae, nine were not recovered and two patients had unknown outcome. In five patients the dose was not changed and one of them was reported as recovered, another one as outcome unknown, and three as outcome not recovered. In four patients out of 31, the action taken with the drug and the outcome were given as unknown.

Literature and Labelling

The profound immunosuppressive effect of TNF-α inhibitors has long been suspected to increase the risk of certain types of neoplasm such as lymphoproliferative disorders. In the United Kingdom and the US, the Summary of Product Characteristics (SmPC) for adalimumab, skin cancer is mentioned, excluding melanoma (including basal cell carcinoma and squamous cell carcinoma) but noting benign neoplasm as a common adverse reaction. Solid organ neoplasms (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma, and lymphoma are also described as uncommon reactions. It is noted that lymphoma is mentioned in the warning section.[11, 12]

In the infliximab SmPC lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer, are mentioned as having a rare frequency. Hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease or ulcerative colitis), and Merkel cell carcinoma, with frequency not known, are also listed.[13, 14]

In the etanercept SmPC non-melanoma skin cancers are described as uncommon, with malignant melanoma, lymphoma, leukaemia as rare, and Merkel cell carcinoma with an unknown frequency.[15, 16]

It is worth noting that these products have biosimilars on the market, and the SmPCs of biosimilars describe neither cutaneous lymphoproliferative disorders nor LyP.[17–22]

In the literature there are two more case reports that analyze the potential association of LyP and adalimumab and infliximab. The first report describes a 21 years-old man, he was on treatment with infliximab and azathioprine over 2 years for inflammatory bowel disease and developed abdominal pain associated with anorexia and a 10-pound weight loss, and also, scattered violaceous papular nodules erupted on his extremities and buttocks.[23] The second case, mention a 28-year-old man with rheumatoid arthritis, whom the adalimumab therapy was considered to control his autoimmune disease after use of several treatments to control his condition, the symptoms were observed after 6 months of initiated the adalimumab therapy. His skin lesions were described as erythematous to brown

nodules on the elbow and upper arm[24]. Both cases highlight the careful follow-up that should be done to patients with inflammatory disease and use of TNF-α inhibitors.

Discussion

Reports in VigiBase suggest that there is a possible signal for the association of etanercept, infliximab and adalimumab with LyP. These TNF-α inhibitors were the only suspected drugs in 24 out of 31 cases.

There were reports with azathioprine and methotrexate as co-suspected drugs, and there is a known association of these drugs with lymphoproliferative disorders but not with LyP. This finding can be taken as a confounder, but at the same time, it could suggest that the concomitant use of TNF-α inhibitors and methotrexate or azathioprine in some (high-risk) patients is associated with the occurrence of LyP or other lymphoproliferative disorders. In this case series, eleven patients describe use of metothrexate or azatiophrine, however in only 7 cases these medications were mentioned as co-suspected. In 5 patients out of 11 other lymphoproliferative malignancies were also described (case 2, 6, 16, 25, 29). Only in 2 cases of 11, the starting dates were mentioned to clarify the concurrent use at the moment of initial LyP symptoms (2 and 20).

The more aggressive the inflammatory condition the more intensive is the pharmacological treatment is, for this reason, patients treated with more biologicals may have a higher risk to develop lymphoproliferative disorders, for example in the cases 1 and 2, where it is possible to envisage the baseline condition as the principal cause of the event. However, they are just two patients out of 31 in the case series.

Because LyP could be considered an indolent lymphoma, a longtime to onset (median 16 months) is compatible with the clinical development of LyP and raises the hypothesis that this adverse reaction is associated with chronic use of TNF-α inhibitors drugs. The biological plausibility is likely due to the down-regulation of innate and adaptive immunity by the TNF-α inhibitor therapy.[5, 7] In the cases with a shorter time to onset, other risk factors must be accounted for, such as severe baseline condition and other pharmacological drugs used, as well as immunocompromised patients, especially those with solid organ or bone marrow transplantation, however this information is lacking.

Dechallenge is not supportive of a drug-adverse effect association, because LyP is a recurrent disease. However, in 19 patients out of 31 the drug was withdrawn and there was an improvement in eight (three recovered, three recovering and two recovered with sequelae). Nonetheless, in the remaining 11 of these 19, the outcome was not recovered (nine cases) and unknown (two cases).

As LyP can appear in any part of the body, without relation with the site of injection, and is characterized by skin lesions which come and go, LyP could be considered as a chronic disease or, in the worst scenario, an indolent lymphoma. In a retrospective study, the French Study Group on Cutaneous Lymphoma identify and follow 52 cases of LyP over 13 years, they suggest that up to 20% of patients with LyP might develop into lymphoma. Also, based on their research, they suggest the detection of a monoclonal rearrangement of the T-Cell Receptor gene in skin lesions from patients with LyP is a major risk factor for the occurrence of an associated lymphoma[2]. It is important to bear in mind the controversy regarding the association of autoimmune conditions with lymphoproliferative disorders. The B-cell responses in rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, and Hashimoto's thyroiditis are associated with lymphoma. T-cell responses in coeliac disease, Crohn's disease, ulcerative colitis, and polymyositis/dermatomyositis are more associated with T-cell lymphoproliferative disorders.[25] Another multicenter cohort study of patients with LyP has suggested an association of 15% of hematological malignancies after 25 years of follow-up.[26] This should be considered for patients with LyP because of the overlap with MF or other types of cutaneous lymphoma. For these reasons, a careful follow-up should be performed in such patients to quickly identify complications.

The Therapeutic Goods Administration from Australia in 2018, identified a safety signal based on three local adverse event reports, and working together with the sponsor of the innovator brand, they updated the SmPC of the product including MF in the neoplasm benign and malignant adverse reaction section, with a rare frequency. This could strength this signal,

considering MF is a cutaneous T cell lymphoma, and LyP is defined as a primary cutaneous CD30+ lymphoproliferative disorder.[27]

Pharmacovigilance in biological drugs is challenging. For this reason, the potential association of LyP and TNF-α inhibitors could have a high impact in clinical practice. So far, LyP and other lymphoma cutaneous are not described as adverse reactions of adalimumab, etanercept or infliximab.

Conclusion

The reports in VigiBase revealed a pattern in the occurrence of LyP after the use of infliximab, adalimumab, etanercept. These TNF-α inhibitors were the only suspected drug in 24 out of 31 reports. The median time to onset was 16 months, and this was related to the nature of the adverse reaction and the drug action mechanism. LyP or cutaneous T cell lymphoma is not labelled in the SmPC of these products, although there is literature published that support this signal. For these reasons, it seems the addition of LyP to the product labelling of adalimumab, etanercept, and infliximab (TNF-α inhibitors drugs) could be considered, so that both physicians and patients are aware of this condition during the treatment with these drugs.

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Table 1. Characteristics of case reports in VigiBase of Tumour Necrosis Factor- α inhibitors in association with lymphomatoid papulosis

Case	Age/ Sex	Suspected (S), Interacting (I) or concomitant (C) drugs	Therapeutic indication for Tumour Necrosis Factor-α inhibitors / dose	Duration of use TNF-α inhibitors	Reactions (MedDRA preferred terms)	Time to onset	Action taken with drug / Outcome of LyP
1	38/M	Adalimumab, Infliximab, Azathioprine (all S)	Crohn's disease/ Adalimumab: 40mg SC every 2 weeks	A: 18 months I: 12 months	Lymphomatoid papulosis, Ichthyosis	A: 18 months	Withdrawn/ Recovered with sequelae
2	16/F	Etanercept 1st biologic used), Adalimumab 2nd biologic, Infliximab 3rd biologic, Azathioprine, Cyclophosphamide, Methotrexate, Rituximab, Abatacept (all S), Acetylsalicylic acid, Omeprazole, Prednisolone (all C)	Vasculitis Etanercept: 25 mg SC twice in a week Adalimumab: 40mg SC every 2 weeks Infliximab: 300 mg IV every 4 weeks	E: 2 months A: 14 months I: 2 months	Lymphomatoid papulosis, Lymphoma	E: 4 years A: 2 years I: 1 year	Withdrawn/ Not recovered
3	69/ Male	Infliximab (S), Paracetamol, Celecoxib, Amlodipine, Hydrochlorothiazide, Omeprazole (all C)	Ankylosing spondylitis/500 mg IV every 8 weeks *Previous doses 300 mg*	Unknown	Lymphomatoid papulosis	12 months* described in narrative	Unknown/ Unknown
4*	56/ Male	Inliximab (S)	Psoriasis/5 mg/kg IV	Unknown	Lymphomatoid papulosis, Anaplastic large cell lymphoma T- and null-cell types	Unknown	Withdrawn/ Not recovered
5	21/M	Infliximab (S), Azathioprine (C)	Crohn's disease/5 mg/ kg IV per 12 weeks	Unknown	Lymphomatoid papulosis	Unknown	Withdrawn/ Recovered
6	53/M	Infliximab (S), Folic acid, Methotrexate (Both C)	Psoriasis/5 mg/kg IV	Unknown	Lymphomatoid papulosis, Cutaneous T-cell lymphoma (LLT: Mycosis fungoides), Skin lesion	4 months	Dose not change/ Unknown
7*	58/M	Infliximab (S)	Crohn's enteritis/IV every 2 months	12 years	Lymphomatoid papulosis	10 years	Withdrawn/ Unknown

Case	Age/ Sex	Suspected (S), Interacting (I) or concomitant (C) drugs	Therapeutic indication for Tumour Necrosis Factor-α inhibitors / dose	Duration of use TNF-α inhibitors	Reactions (MedDRA preferred terms)	Time to onset	Action taken with drug / Outcome of LyP
8	65/F	Adalimumab (S), Omeprazole, Acetylsalicylic acid, Calcium, Colecalciferol, Bumetanide, Losartan, Iron, Vitamins nos, Atropine, Diphenoxylate, Magnesium citrate, Metformin, Atorvastatin, Potassium (all C)	Crohn's disease/40 mg SC every 2 weeks		Lymphomatoid papulosis, Squamous cell carcinoma of skin, Arthralgia, Muscle twitching, Angina pectoris, Complement factor C4 decreased, Cough, Chest discomfort, Antinuclear antibody increased, Rash erythematous, Ejection fraction decreased, Bronchitis, Rash pruritic, Pyrexia, Injection site pain, Asthenia, Scab, Rash macular, Cardiac failure congestive, Dyspnoea	Unknown	Dose not change /Not recovered
9	37/M	Adalimumab, Azathioprine (both S), Budesonide (C)	Crohn's disease/40 mg SC every 2 weeks	1 year and 6 months	Lymphomatoid papulosis	17 months	Withdrawn/ Recovering
10*	56/F	Adalimumab (S)	Unknown/Unknown	Unknown	Lymphomatoid papulosis	Unknown	Unknown/ Recovered
11*	56/F	Adalimumab (S), Naproxen (C)	Rheumatoid arthritis/ Unknown	Unknown	Lymphomatoid papulosis, Large-cell anaplastic non- Hodgkin lymphoma	2,6 months	Dose not change/ Recovered
12	-/-	Adalimumab (S)	Rheumatoid arthritis / SC *No more information*	Unknown	Lymphomatoid papulosis	24 months	Wwithdrawn/ Unknown
13	25/M	Adalimumab (S)	Crohn's disease/40 mg SC every 2 weeks	4 years	Lymphomatoid papulosis, T-cell lymphoma, Rash papular	4 years	Withdrawn/ Not recovered
14*	21/F	Adalimumab (S)	Crohn's disease/SC every 2 weeks	16 months	Lymphomatoid papulosis, Skin lesion	16 months	Withdrawn/ Not recovered

Case	Age/ Sex	Suspected (S), Interacting (I) or concomitant (C) drugs	Therapeutic indication for Tumour Necrosis Factor-α inhibitors / dose	Duration of use TNF-α inhibitors	Reactions (MedDRA preferred terms)	Time to onset	Action taken with drug / Outcome of LyP
15	61/F	Adalimumab (S), Alendronic acid, Losartan, Potassium, Diclofenac, Hydroxychloroquine (all C)	Psoriasis/40 mg SC every 2 weeks	Unknown	Lymphomatoid papulosis, Rash	Unknown	Dose not change/Not recovered
16	51/F	Adalimumab (S), Azathioprine, Analgesics not specified (Both C)	Rheumatoid arthritis/40 mg SC every 2 weeks	1 month	Lymphomatoid papulosis, Anogenital warts, Molluscum contagiosum, Anaplastic large cell lymphoma T- and null-cell types	24 days	Unknown/ Unknown
17	49/F	Adalimumab (S), Methotrexate (C)	Psoriatic arthritis/40 mg SC every 2 weeks	Unknown	Lymphomatoid papulosis	Unknown	Withdrawn/ Not recovered
18*	38/M	Azathioprine, Adalimumab (both S)	Crohn's disease/40 mg every 2 weeks	Unknown	Lymphomatoid papulosis	Unknown	Withdrawn/ Recovered
19*	38/M	Adalimumab (S)	Crohn's disease/40 mg biweekly	Unknown	Lymphomatoid papulosis	Unknown	Withdrawn/ Recovered with sequelae
20	48/M	Adalimumab, Methotrexate (both S)	Ankylosing spondylitis/40 mg SC every 2 weeks	Unknown	Lymphomatoid papulosis	8 months	Dose not change/Not recovered
21	-/M	Etanercept (S), Naproxen (C)	Psoriasis/50 mg SC twice in a week	3 months	Lymphomatoid papulosis, Pityriasis lichenoides et varioliformis acuta	Unknown	Withdrawn/ Not recovered
22	-/ Male	Etanercept (S)	Ankylosing spondylitis/50 mg per year *No more information*	19 months	Lymphomatoid papulosis	18 months	Withdrawn/ Recovering
23	-/ Male	Etanercept (S)	Psoriasis/50 mg SC twice in a week	6 months	Lymphomatoid papulosis	5 months	Withdrawn/ Recovering
24	-/F	Etanercept (S), Methotrexate (C)	Rheumatoid arthritis/50 mg SC weekly	23 months	Lymphomatoid papulosis	Unknown	Withdrawn/ Not recovered
25	82/F	Etanercept, Methotrexate (both S), Celecoxib (C)	Rheumatoid arthritis/SC weekly	8 years	Cutaneous T-cell lymphoma (LLT: Mycosis fungoides), Lymphomatoid papulosis	Unknown	Withdrawn/ Not recovered
26*	53/ Male	Etanercept (S)	Psoriasis/25 mg twice in a week	Unknown	Lymphomatoid papulosis, Drug ineffective	Unknown	Withdrawn/ Recovered

Case	Age/ Sex	Suspected (S), Interacting (I) or concomitant (C) drugs	Therapeutic indication for Tumour Necrosis Factor-α inhibitors / dose	Duration of use TNF-α inhibitors	Reactions (MedDRA preferred terms)	Time to onset	Action taken with drug / Outcome of LyP
27	-/ Male	Etanercept (S)	Psoriasis/SC	Unknown	Lymphomatoid papulosis	Unknown	Withdrawn/ Not recovered
28*	41/M	Etanercept (S)	Unknown/Unknown	Unknown	Lymphomatoid papulosis, Cutaneous T-cell lymphoma stage IV (LLT: Mycosis fungoides)	Unknown	Unknown/ Recovered
29*	41/M	Azathioprine, Thalidomide, Etanercept, Interferon (all S)	Dermatitis exfoliative generalised/Unknown	Unknown	Lymphomatoid papulosis, Cutaneous T-cell lymphoma (LLT: Mycosis fungoides)	Unknown	Unknown/ Recovered
30	59/F	Etanercept (S)	Rheumatoid arthritis/50 mg SC weekly	Unknown	Lymphomatoid papulosis, Contusion, Rash, Injection site erythema, Injection site reaction	Unknown	Unknown/ Unknown
31	59/F	Etanercept (S)	Rheumatoid arthritis/ Unknown	Unknown	Lymphomatoid papulosis	Unknown	Unknown/ Unknown

**Published case report. SC Subcutaneous. IV intravenous*

SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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