The utilisation of a new tool in signal management – **WHODrug Standardised Drug Groupings**

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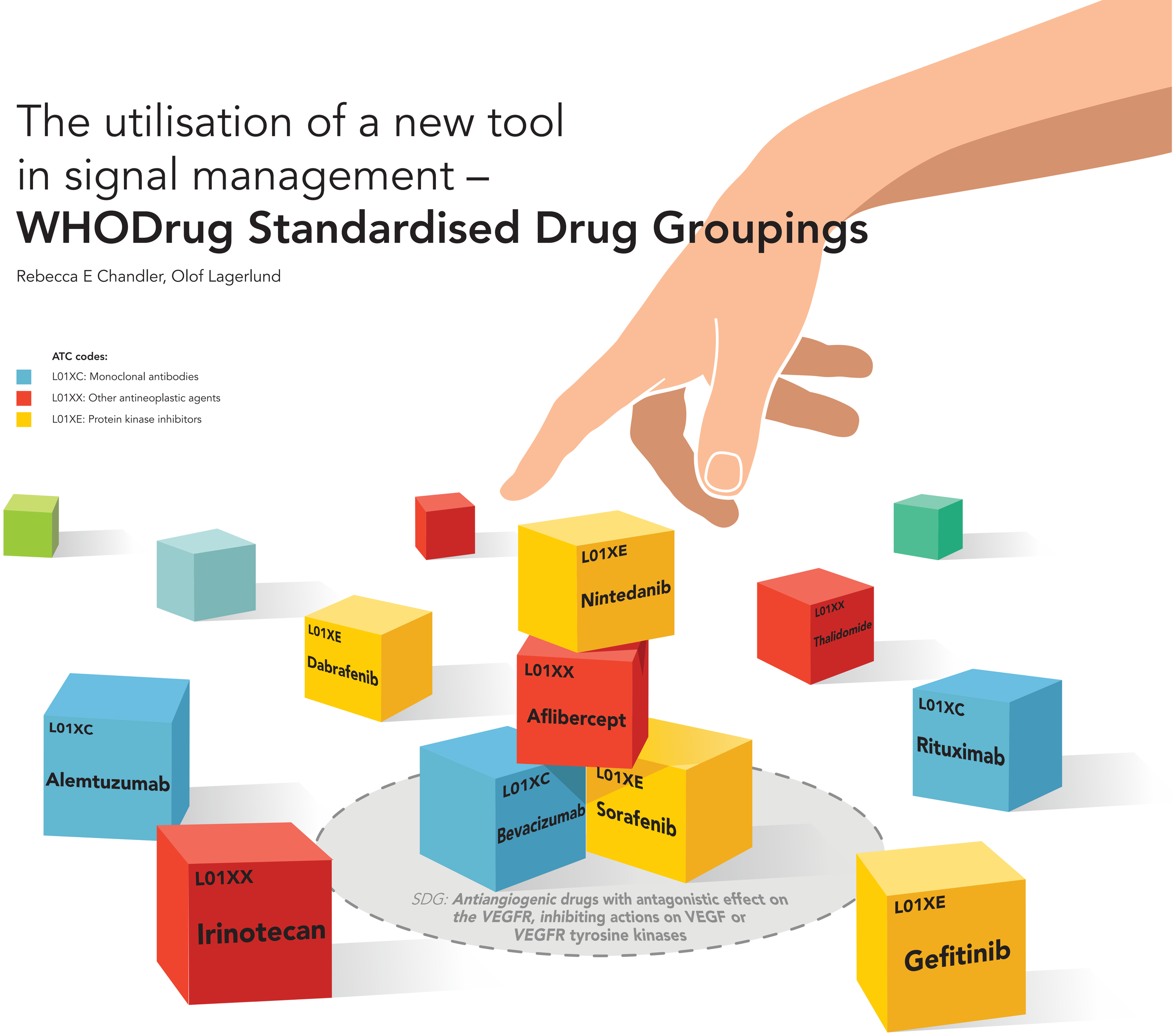

Background

Screening of large databases of spontaneous reports of suspected adverse drug reactions (ADR) is performed by disproportionality analyses at the level of single drug – ADR pairs. Subsequent signal refinement may include exploration of additional clinically relevant concepts within the MedDRA hierarchy and potential drug class effects with Anatomical Therapeutic Classification (ATC). WHODrug Standardised Drug Groupings (SDG) are specific classifications of drugs of interest, grouped according to properties such as their pharmacological effect or metabolic pathway.

Objectives

To demonstrate the utility of an SDG in the refinement of a signal of nintedanib – colitis identified by statistical screening of VigiBase.

Methods

Disproportionality analysis was performed on 13 February 2019 in VigiBase, the global database for individual case safety reports; the combination of nintedanib – colitis (MedDRA PT) was highlighted with an IC_{025} of 0.96. An initial clinical review was undertaken to determine the need and/or direction of signal refinement within VigiBase data. Disproportionality analyses were performed for relevant adjacent terms in the MedDRA dictionary, as well as for drug groupings using both the ATC and SDG.

Results

Clinical review revealed nintedanib to be a small molecule tyrosine kinase (TK) inhibitor blocking vascular epithelial growth factor (VEGF), fibroblast GF and platelet-derived GF receptors. A mouse model reveals VEGF inhibition to be associated with regression of capillaries in intestinal villi, and gastrointestinal perforation is included in the Summary of Product Characteristics. Subsequent exploration of adjacent MedDRA PTs revealed an IC_{025} of 0.02 for "colitis ischaemic" and 2.22 for "gastrointestinal perforation". Nintedanib is in ATC code LO1XE "Protein kinase inhibitors" and in the SDG "Antiangiogenic drugs with antagonistic effect on the VEGFR, inhibiting actions on VEGF or VEGFR TKs". Respective disproportionality at ATC level was IC_{025} 0.04 for "colitis ischaemic" and IC_{025} 2.34 for "gastrointestinal perforation"; at the SDG level was IC_{025} 1.23 and IC_{025} 5.37.

Conclusions

Standardised drug groupings are a useful tool in the signal management process. Refinement of the signal "nintedanib-colitis" using an SDG provided stronger evidence of a potential causal relationship compared to ATC. Exploration of potential drug class effects during signal assessment may be improved by use of WHODrug SDG.

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