EDITORIAL

Why a case report is more than just an unexpected observation

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Clinical trials only detect frequently occurring adverse events, and the detection of rarer adverse events depends on experience gained during the period after marketing of a drug. At this point in time the drug is used under real-life circumstances and in large groups of patients.

Although post-marketing clinical studies are also designed to study safety, there is a key role for reporting presumed adverse events. Reporting of serious adverse events to the local regulatory authorities (e.g. Netherlands Pharmacovigilance Centre Lareb in the Netherlands) is required by law, also outside clinical trials. However, case reports with adverse events published in medical literature also form an important contribution to pharmacovigilance.[1] After all, the publication of the first report on congenital deformations after maternal use of thalidomide, published in the Lancet in 1961,[2] stood at the beginning of drug safety legislation and the formation of the regulatory authorities that we know today.

Nowadays, almost 60 years later, spontaneous reports are still vital in decision-making during the life cycle of a drug after marketing. Nineteen drugs were withdrawn from the European market between 2002 and 2011 for safety reasons, based on information mostly provided by case reports.[3] Reports on adverse events are not only important for monitoring the safety profile of a drug, but can also give insight into pharmacological pathways and the mechanism of action of a drug. This helps to clarify our understanding of the pathophysiology of certain diseases.

In this issue of the Netherlands Journal of Medicine, Muller-Hansma and colleagues present a case of an adolescent boy who was diagnosed with acute lymphoblastic leukaemia for which he was treated with dasatinib, a tyrosine kinase inhibitor (TKI).[4] During this treatment he developed proteinuria, oedema and hypalbuminaemia; events that were already listed in the product leaflet of dasatinib. Recently, nephrotic syndrome was added.[5] One could argue that the presented case does not fulfil all the criteria for nephrotic syndrome, since the reported proteinuria is not in the nephrotic range (<3.5 grams/24 hours). However, the clinical symptoms in this case in combination with the presented spontaneous reports from Eudravigilance and case reports from literature do provide sufficient support to include nephrotic syndrome as a separate adverse event.

In the presented case, the time course and the swift recovery of the symptoms when the drug was stopped contributes to a high likelihood of causality.[6] It is likely that nephrotic syndrome is a class effect of the TKIs, since it has been described in other TKIs, such as imatinib and sunitinib, as well.[7] A clear hypothesis on the pathophysiological pathway linking treatment with TKIs and nephrotic syndrome exists through its effect on vascular endothelial growth factor (VEGF).[8] The role of targeting VEGF as antitumour therapy and its renal effects have been reviewed in this journal before.[9] Anti-VEGF treatment affects VEGF production, and results in endothelial damage and loss of nephrin. The resulting malfunction of the glomerular filtration apparatus will ultimately lead to the development of nephrotic syndrome. Nephrotic syndrome has also been associated with the use of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) in the treatment of metastatic melanoma, in which VEGF inhibition also plays an important role.[10] These types of reports help in understanding the pathophysiology of the adverse events associated with targeted therapies.

Not only the treatment of a malignancy may be associated with the development of nephrotic syndrome, but the malignancy itself can cause glomerular disease including nephrotic syndrome as well.[11] Chronic lymphocytic leukaemia, for which dasatinib is registered, is associated with membranoproliferative glomerulonephritis and nephrotic syndrome.

Treatment options in oncology have increased in the last decades. TKIs are increasingly prescribed, but also

the use of immunotherapy is emerging. In both, renal adverse events including nephrotic syndrome have been reported.[12,13]

In most cases of nephrotic syndrome associated with treatment with TKIs, symptoms resolved spontaneously after discontinuing the drug, and further treatment was not necessary. Renal adverse events in nivolumab and pembrolizumab (both PD-1 inhibitors), both examples of immunotherapy, however, may need immunosuppressive treatment, depending on the severity of the symptoms.[12,13] Screening for immunological adverse events, including nephritis, is standard care during these treatments.

With the increasing use of targeted therapies, clinicians should be aware of the development of new types of adverse events which may also affect the kidney. The introduction of these targeted therapies for a broad spectrum of diseases has involved prescribers from many different medical backgrounds. Awareness of the potential for localized and sometimes atypical adverse events may not always be present. Due to the fact that case reports are typically descriptions of small numbers of observations, without ingenious methodological study design or statistical analysis, they are at the bottom of the hierarchy of clinical evidence. However, as illustrated with the examples on nephrotic syndrome, we emphasise that case reports do have an important role in medical research and continuous medical education.

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