Dasatinib and nephrotic syndrome

Introduction

Dasatinib (Sprycel®) is indicated for adults for *newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML), Ph+ acute lymphoblastic leukemia (ALL)* and *CML in the chronic, accelerative or blastic phase resistant to previous therapy including imatinib.*
Dasatinib belongs to the group of proteinkinase inhibitors. The mechanism of action is inhibition of BCR-ABL-kinase, kinases from the SRC family and several other oncogenetic kinases including c-KIT, ephrin (EPH) receptorkinases en PDGFß receptor.
Dasatinib was granted marketing authorization in the Netherlands in 2006 [1].

CML is a myeloproliferative neoplasm, characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with fairly normal differentiation [2]. In general there are three disease phases, the chronic stable phase (a relatively indolent condition), the accelerated phase (the more aggressive condition) and the blast crisis [3].
ALL is a lymphoid neoplasm which shows a progressive disease course, where symptoms in precursor B-cel ALL may progress over weeks to months with others presenting even more acutely [4].
The Philadelphia (Ph) chromosome refers to a balanced translocation between chromosomes 9 and 22 that can be present in CML and ALL, resulting in BCR-ABL1 fusion. Subsequent BCR-ABL1 activity promotes uncontrolled proliferation of transformed cells [5].

Nephrotic syndrome can have various causes and is defined by the presence of heavy proteinuria (protein excretion greater than 3.5 g/24 hours), hypoalbuminemia (less than 30 g/L), and peripheral oedema [6]. Proteinuria results from defects in the capillary wall of the glomeruli, that consists of the fenestrated capillary endothelium, the glomerular basement membrane and the podocytes (the endothelial cells in the glomeruli) [7].

Report

On 4 May 2016 the Netherlands Pharmacovigilance Centre Lareb received one report of nephrotic syndrome with the use of dasatinib. In this case dasatinib was used off label, being administered to a child.

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This serious spontaneous report (hospitalisation for 11 days) from a specialist doctor concerns a boy aged 11-20 years, with nephrotic syndrome (with oedema, hypoalbuminemia (lowest level measured 20 g/L) and proteinuria) following administration of dasatinib, once daily 70 mg, for Ph+ common acute lymphoid leukaemia with a latency of 25 days after start. The patient also had neutropenia, fever and low immunoglobulin levels. The drug dasatinib was withdrawn. The patient was treated with intravenous antibiotics, analgesics, immunoglobulins, fluids and parenteral nutrition. The patient recovered from the nephrotic syndrome one week after withdrawal of dasatinib. Concomitant medications were mercaptopurine, itraconazole, macrogol, valaciclovir, midazolam, omeprazole, flumazenil, ciprofloxacin, granisetron and tramadol.
The medical history indicates that the patient received cytarabine and mercaptopurine* chemotherapy according to the EsPhALL protocol [8].

*The Dutch SmPCs of cytarabine and mercaptopurine do not report nephrotic syndrome or proteinuria as an adverse reactions [9,10].

Other sources of information

SmPC

The Dutch SmPC of dasatinib mentions proteinuria as a sometimes occurring adverse reaction. Nephrotic syndrome is not mentioned as an adverse reaction [1].

In the Dutch SmPCs of the other BCR-ABL-kinase inhibitors imatinib, nilotinib and ponatinib, neither nephrotic syndrome nor proteinuria are mentioned as adverse reactions [11-13].

Concerning other tyrosine kinase inhibitors nephrotic syndrome is a labelled adverse reaction for sorafenib and sunitinib, both drugs with therapeutic targets that include vascular endothelial growth factor (VEGF) receptors [14,15].

Literature

A nine-month-old girl was diagnosed with Ph+ CML. She was treated with imatinib for a year and was then switched to dasatinib 60 mg/m^2 because of BCR-ABL positivity. At the age of three years, the patient developed nephrotic syndrome. Electron microscopy of a renal biopsy showed partial glomerular epithelial foot process effacement and focal capillary loop collapse with basement membrane wrinkling. She was treated and the reaction improved, but only after withdrawal of dasatinib the patient recovered from the reaction [16].
A five-year-old boy with Ph+ ALL developed nephrotic syndrome 26 days after hematopoietic stem cell transplantation while using dasatinib (dose not reported). At electron microscopy most foot processes were fused, which could indicate minimal change disease. Within a week after withdrawal of dasatinib, the nephrotic syndrome resolved [17].
A 63-year-old woman with CML experienced nephrotic-range proteinuria, while using dasatinib 100 mg per day. Kidney biopsy showed evidence of chronic thrombotic microangiopathy. The patient recovered from the proteinuria after switching to imatinib [18].
A 64-year-old woman with Ph+ ALL used dasatinib in addition to a regimen of chemotherapy comprising cyclophosphamide, daunorubicin, vincristine, prednisolone, methotrexate, cytarabine and dexamethasone. Two weeks after dose increase from 110 mg to 140 mg daily of dasatinib, she developed nephrotic syndrome. After withdrawal of dasatinib the nephrotic syndrome resolved within a week. Dasatinib was restarted in a lower dose of 70 mg daily without recurrence of nephrotic syndrome [19].
One literature case was described in Eudravigilance (case AG), but the original article was not available through Pubmed. This case concerned a fourteen-year-old male patient with Salmonella sepsis and nephrotic syndrome receiving treatment with dasatinib 60 mg/m^2 for ALL with a latency of ten months. The reaction was treated with fluid restriction, diuretics and albumin infusions. Five weeks later the patient developed chylothorax. Dasatinib was withdrawn and a low-fat diet was started. Within two weeks, the chylothorax resolved. Dasatinib was restarted at a reduced dose of 48 mg/m^2/day instead of 60 mg/m^2 without recurrence of nephrotic syndrome and chylothorax [20,21].

Databases

Table 1. Reports of the PT “nephrotic syndrome” and “nephrotic syndrome” associated with dasatinib, in the Lareb [22], WHO [23] and Eudravigilance database [20]. Lareb received no reports of nephrotic syndrome associated with imatinib, nilotinib or ponatinib

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Nephrotic syndrome	1	
WHO	Nephrotic syndrome	21	5.4 (3.5-8.3)
Eudravigilance	Nephrotic syndrome	31**	6.6 (4.6– 9.4)

*** The number of cases is higher in the Eudravigilance database compared to the WHO database. The exact cause of this is unknown to us, but is probably based on administrative reasons (such as speed of processing). Furthermore the cases include five duplicates, which makes the number of unique reports in Eudravigilance 26.*

Eudravigilance

On 15 December 2016 the Eudravigilance database contained 31 cases of nephrotic syndrome associated with dasatinib. These cases are described in more detail in the addendum.
Ten of the cases (of which five appear to be duplicates of another case) in Eudravigilance concerned literature reports. Literature cases are based on the article of Lim *et al* [17], *Ruebner et al* [16],

Wallace *et al* [18]), Hirano *et al* [19] and Chow *et al* [21]. All these cases are described at the section "Literature" in this report.

A summary of the eight strongly supportive cases from Eudravigilance excluding the literature cases are described here:

Seven cases concerned female patients and one a male patient. One case concerned a child, the other cases were all adult patients. The ages varied between 13 and 70 years. The median age was 40 years. The latencies varied from about one month to seven months and there was one case with a very long latency of almost five years. In one case latency was unknown. Seven patients recovered from the reaction, where in two patients treatments were reported. Of one report outcome was unknown. In one case (case AA) a positive rechallenge was reported. In two reports results from renal biopsy were described: in one case there was membranous glomerulonephritis and in one case there was focal segmental glomerulosclerosis at electron microscopy.

Prescription data

The number of patients using dasatinib in the Netherlands cannot be indicated by use of the GIP database (the database in the Netherlands providing information on drug use based on data of the health insurance companies), because dasatinib is currently provided by hospital pharmacies [24].

Mechanism

A possible mechanism is by disrupting the VEGF signaling pathway through inhibition of the SRC family kinases. VEGF expression occurs in human podocytes and is involved in maintaining normal glomerular function [18]. Disrupting VEGF signaling through therapy targeting VEGF or through inhibition of the VEGF receptors, is associated with minimal change nephrotic syndrome which may evolve to focal and segmental glomerulosclerosis, and thrombotic micro-angiopathy in the glomerular and peri-tubular capillaries [25]. Proteinuria after inhibition of VEGF signalling is considered a dose-related side-effect [26].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received one case of nephrotic syndrome associated with dasatinib for ALL in a child. This concerned off label use of dasatinib because the drug is indicated for adults. Lareb received no reports of nephrotic syndrome in one of the other BCR-ABL kinase inhibitors. The literature provides several other supportive cases of nephrotic syndrome associated with dasatinib, of both children and adults. The Eudravigilance database contains at least another eight strongly supportive cases indicative for nephrotic syndrome as an adverse reaction of dasatinib. In three of the cases it is reported that after restarting dasatinib at a lower dose, the nephrotic syndrome did not reoccur (the case described by Hirano *et al*, by Chow *et al* and case P in Eudravigilance [19-21]). Nephrotic syndrome is labeled for some of the tyrosine kinase inhibitors with the VEGF receptor as one of their major target receptors [14,15]. There is a possible mechanism for dasatinib described in the literature by inhibiting the SRC family kinases resulting in disruption of the VEGF signaling pathway.
Based on the report received by Lareb and the other cases in Eudravigilance, supported by the literature, it is suggested that dasatinib might cause nephrotic syndrome and that this might be a dose-dependent effect.

References

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This signal has been raised on February 2017. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl