

Nilotinib as a risk factor for ischaemic stroke: a series of three cases[☆]



Nilotinib como factor de riesgo de ictus isquémico. A propósito de 3 casos

Dear Editor,

Nilotinib is a tyrosine kinase inhibitor (TKI) that has been approved as a treatment for chronic myeloid leukaemia (CML). Nilotinib has been associated with increased risk of peripheral artery disease (PAD),^{1–3} coronary artery disease, and cerebrovascular events.^{4–6} We present the cases of 3 patients who experienced ischaemic strokes during long-term treatment with nilotinib. Two of them also presented PAD and intracranial atherosclerosis. The third had dissection of the internal carotid artery (ICA) with no evidence of atheromatosis in the vascular study. At the time of stroke, the 3 patients showed high 10-year cardiovascular risk (CVR) according to the instrument developed by the American Heart Association (AHA).⁷

Description of the 3 cases

Case 1

Our first patient was a 66-year-old man with a history of arterial hypertension and CML; he had been treated with nilotinib 400 mg twice daily throughout the previous 8 months. His 10-year risk of atherosclerotic cardiovascular disease (ASCVD) was 9.6%. The patient visited our hospital due to sudden onset of vertigo, diplopia, central facial palsy, and gait ataxia. An MRI scan revealed multiple acute ischaemic lesions in the midbrain, pons, and occipital cortex. MR angiography (MRA) showed occlusion of the vertebral artery and significant intracranial atherosclerosis (Fig. 1A). Treatment was changed to dasatinib and oral anticoagulant treatment with acenocoumarol was added. Eight months later, the patient was diagnosed with PAD and had a stent placed in his femoral artery.

Case 2

The second patient was a male smoker aged 56 with a history of arterial hypertension and coronary artery disease. Five years before the admission in question, he was diagnosed with CML and treated with nilotinib 300 mg twice daily. Sixteen months before being admitted, the patient presented occlusion of the central retinal artery. Treatment with nilotinib was therefore suspended in favour of antiplatelet and lipid-lowering agents. His 10-year ASCVD risk was 14.8%.

The patient was admitted following multiple self-limiting episodes of dysarthria, hemiparesis, and hemihypaesthesia. The vascular study showed near occlusion of the left ICA and stenosis of the right ICA and both middle cerebral arteries (MCA). We initiated anticoagulant treatment with intravenous sodium heparin. Despite treatment, the patient showed further symptoms of hemiplegia and aphasia due to left ICA occlusion. Emergency angioplasty and stent placement failed to result in clinical improvement. An ultrasound study 2 days later showed stent occlusion. MR angiography confirmed lack of flow in the left ICA and MCA. The patient remained on anticoagulant treatment with acenocoumarol after discharge. His NIHSS score was 7 in a follow-up assessment completed at 3 months. He had not experienced any new vascular events at that time and we decided to replace acenocoumarol with aspirin.

Case 3

Our third patient was a 66-year-old man with a history of CML treated with nilotinib 300 mg twice daily throughout the previous 7 years. The patient visited our department due to 2 transient episodes of hemiparesis and left hemihypaesthesia. His 10-year ASCVD risk was 9.3%. An MRI scan revealed multiple ischaemic lesions in the right frontal and parietal cortex. MR angiography showed ICA dissection and MCA stenosis of more than 50% (Fig. 2A and B). After suspending treatment with nilotinib, we started treating the patient with lipid-lowering drugs and acenocoumarol as an anticoagulant agent. At 3 months, a follow-up CT angiography showed persistent ICA occlusion and we opted to replace acenocoumarol with aspirin.

Discussion

Nilotinib has been proven to be an effective treatment for CML.⁸ Nevertheless, long-term follow-up studies have documented such vascular events as PAD, coronary artery disease, or cerebrovascular disease in a significant percentage of patients receiving this treatment.^{9,10} Several mechanisms have been proposed to explain this association. The effects of nilotinib on nonhematopoietic cells, such as vascular and perivascular cells, mast cells, or pancreatic cells, might promote development of atherosclerosis, hyperglycaemia, or hypercholesterolaemia.² Furthermore, the TKI ponatinib has been associated with vascular and cerebral events, which suggests a potential drug class effect.^{1,11} However, such events have not been described with imatinib or dantininib.

Two of our patients presented pronounced intracranial atherosclerosis. Similar findings have been described previously in patients treated with nilotinib⁴ and ponatinib.¹¹ The third patient showed dissection of an extracranial large vessel, a manifestation of vascular involvement that had not previously been described in patients treated with nilotinib.

Some experts have suggested that estimating CVR using such validated scales as those developed by the AHA⁷ or the European Society of Cardiology¹² may help identify patients with a higher risk of adverse vascular events.^{1,13}

[☆] Please cite this article as: Gómez-Galván JB, Borrego S, Tovar N, Lull L. Nilotinib como factor de riesgo de ictus isquémico. A propósito de 3 casos. *Neurología*. 2017;32:411–413.

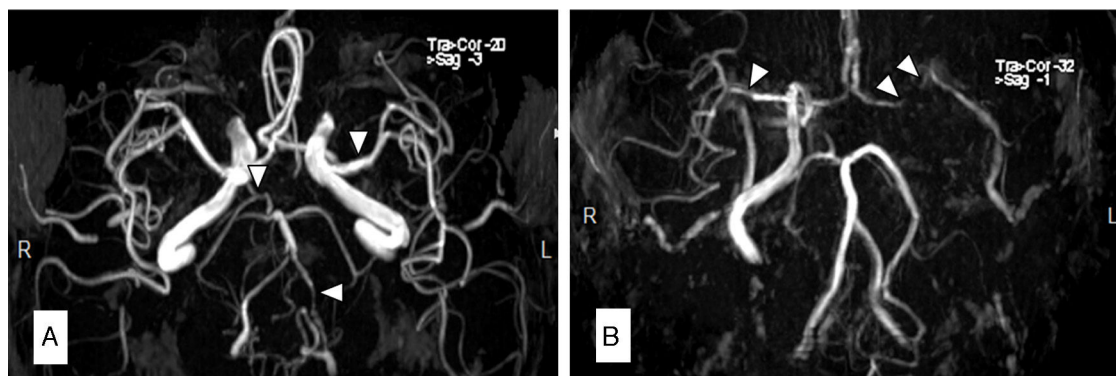


Figure 1 Magnetic resonance angiography (MRA) in patient 1 (A) showed occlusion of the left vertebral artery (VA) and intracranial diffuse atherosclerosis, especially in the right VA, the left MCA, and the right posterior cerebral artery (PCA). The MRA in patient 2 (B) showed a lack of circulation in the left ICA and MCA, with intracranial atherosclerosis predominantly affecting the right MCA and PCA.

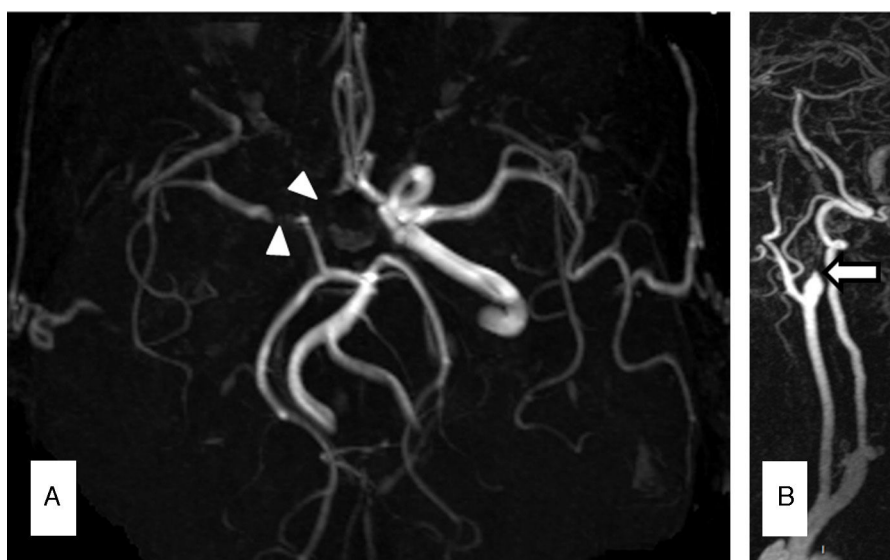


Figure 2 MRA in patient 3 showed moderate stenosis (> 50%) of the right MCA (A) and right ICA occlusion due to dissection (B).

Clinicians should be aware of the association between nilotinib and cerebrovascular events and thus avoid that drug in patients with a high CVR, or else monitor the related metabolic changes that may appear, such as hypercholesterolaemia or hyperglycaemia. Likewise, we recommended informing patients treated with nilotinib about stroke symptoms so that they would know to seek medical attention promptly.

Acknowledgements

We would like to thank Dr Francisco Cervantes for his contributions.

References

1. Valent P, Hadzijušufovic E, Schernthaner G, Wolf D, Rea D, le Coutre P. Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. *Blood*. 2014;125:901–6.
2. Aichberger KJ, Herndlhofer S, Schernthaner GH, Schillinger M, Mitterbauer-Hohendanner G, Sillaber C, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. *Am J Hematol*. 2011;86:533–9.
3. Kim TD, Rea D, Schwarz M, Grille P, Nicolini FE, Rosti G, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. *Leukemia*. 2013;27:1316–21.
4. Coon E, Zalewski N, Hoffman E, Tefferi A, Flemming K. Nilotinib treatment-associated cerebrovascular disease and stroke. *Am J Hematol*. 2013;88:534–5.
5. Quintás-Cardama A, Kantarjian H, Cortes J. Nilotinib-associated vascular events. *Clin Lymphoma Myeloma Leuk*. 2012;12:337–40.
6. Jager N, Stuurman F, Baars J, Opdam F. Cerebrovascular events during nilotinib treatment. *Neth J Med*. 2014;72:113–4.
7. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129:S49–73.

8. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362:2251–9.
9. Giles FJ, Mauro MJ, Hong F, Ortmann CE, McNeill C, Woodman RC, et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. *Leukemia*. 2013;27:1310–5.
10. Gambacorti-Passerini C, How Piazza R. I treat newly diagnosed chronic myeloid leukemia in 2015. *Am J Hematol*. 2014;90:156–61.
11. Mayer K, Gielen G, Willinek W, Müller M, Wolf D. Fatal progressive cerebral ischemia in CML under third-line treatment with ponatinib. *Leukemia*. 2013;28:976–7.
12. Perk J, de Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33:1635–701.
13. Breccia M, Colafigli G, Molica M, Alimena G. Cardiovascular risk assessments in chronic myeloid leukemia allow identification of patients at high risk of cardiovascular events during treatment with nilotinib. *Am J Hematol*. 2015;90:E100–1.

J.B. Gómez-Galván^a, S. Borrego^a, N. Tovar^b, L. Llull^{a,*}

^a *Servicio de Neurología, Hospital Clínic, Barcelona, Spain*

^b *Servicio de Hematología, Hospital Clínic, Barcelona, Spain*

* Corresponding author.

E-mail address: blull@clinic.ub.es (L. Llull).

2173-5808/

© 2015 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Visual impairment due to venous sinus thrombosis in neuro-Behçet's disease[☆]



Pérdida visual debido a trombosis de senos venosos en neuro-Behçet

Dear Editor,

Behçet disease (BD) is a multisystemic inflammatory disease of unknown aetiology characterised by aphthous ulcers in the mouth and genitals, ocular inflammation, skin lesions including erythema nodosum, and acneiform eruptions.¹ Patients may also show neurological, cardiovascular, and gastrointestinal involvement.² Although BD has historically been considered more prevalent in men,³ recent studies point to a more balanced sex ratio.⁴ However, most patients with neurological involvement are men.⁵ BD affects young adults; age at onset is a predictive factor of clinical severity.⁶ Diagnosis is based on the presence of systemic and ocular clinical manifestations, since the disease has no pathognomonic signs. Ocular involvement in patients with BD usually includes bouts of inflammation occurring in the context of an underlying chronic retinal vascular inflammation. Bouts may affect the anterior pole, in the form of acute uveitis, or the posterior pole, with severe vitritis, retinal haemorrhages and exudates, cystoid macular oedema, or optic neuritis.⁷ BD may involve the nervous system in the form of recurrent meningoencephalitis typically affecting the brainstem, idiopathic intracranial hypertension (ICH) with or without sinus thrombosis, cranial mononeuropathies,

cerebellar ataxia, myelitis, seizures, and even cognitive impairment.⁸ There are 2 clearly defined forms of BD: parenchymal and non-parenchymal. The most frequent manifestation of the latter is venous sinus thrombosis.⁹

We present the exceptional case of a patient diagnosed with neuro-Behçet disease (NBD) and rare attacks of ocular inflammation. He displayed bilateral optic atrophy secondary to chronic papilloedema in the context of ICH due to dural venous sinus thrombosis.

Our patient was a 37-year-old white man who was referred to our hospital's neuro-ophthalmology unit due to progressive and persistent vision loss in both eyes over the previous several months. He had been diagnosed with BD at the age of 18 based on the presence of recurrent mouth ulcers since adolescence, 2 bouts of bilateral anterior uveitis, and facial acneiform eruptions. At the age of 24, he was diagnosed with NBD due to thrombosis of the superior longitudinal, transverse, and sigmoid sinuses (Fig. 1) after consulting for symptoms of headache, intermittent vision loss, and papilloedema. He was treated with oral prednisone, azathioprine, colchicine, ciclosporin, and anticoagulants. In the years previous to our evaluation, our patient reported fluctuations in vision quality that were attributed to papilloedema secondary to ICH caused by dural venous sinus thrombosis. Two lumboperitoneal shunts to manage ICH achieved satisfactory results and decreased papilloedema and vision loss fluctuations. Mild papilloedema persisted one year later; doctors suggested a permanent lumboperitoneal shunt placement but the patient refused surgery. He had no other ophthalmological manifestations or relevant family history. At the time of his visit, he was taking oral acetazolamide, azathioprine, antiplatelet agents, and anticoagulant agents. The ophthalmological examination revealed a visual acuity of 0.1 in both eyes. Biomicroscopy showed pigmented keratic precipitates in both eyes and no active signs of ocular inflammation. Intraocular pressure and intrinsic and extrinsic ocular motility were all within normal limits. Eye fundus examination revealed bilateral papillary pallor and no signs of inflammation. The Humphrey visual

[☆] Please cite this article as: Pérez-Bartolomé F, Sanz-Pozo C, Darío Rosati S, Santos-Bueso E, Porta-Etessam J. Pérdida visual debido a trombosis de senos venosos en neuro-Behçet. *Neurología*. 2017;32:413–416.