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Tyrosine Kinase Inhibitors as a New Therapy for Ischemic Stroke and other Neurologic Diseases: Is there any Hope for a Better Outcome?

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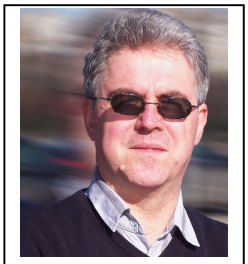

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Abstract: The relevance of tyrosine kinase inhibitors (TKIs) in the treatment of malignancies has been already defined. Aberrant activation of tyrosine kinase signaling pathways has been causally linked not only to cancers but also to other non-oncological diseases. This review concentrates on the novel plausible usage of this group of drugs in neurological disorders, such as ischemic brain stroke, subarachnoid hemorrhage, Alzheimer's disease, multiple sclerosis. The drugs considered here are representatives of both receptor and non-receptor TKIs. Among them imatinib and masitinib have the broadest spectrum of therapeutic usage. Both drugs are effective in ischemic brain stroke and multiple sclerosis, but only imatinib produces a therapeutic effect in subarachnoid hemorrhage. Masitinib and dasatinib reduce the symptoms of Alzheimer's disease. In the case of multiple sclerosis several TKIs are useful, including apart from imatinib and masitinib, also sunitinib, sorafenib, lestaurtinib. Furthermore, the possible molecular targets for the drugs are described in connection with the underlying pathophysiological mechanisms in the diseases in question. The most frequent target for the TKIs is PDGFR which plays a pivotal role particularly in ischemic brain stroke and subarachnoid hemorrhage. The collected data indicates that TKIs are very promising candidates for new therapeutic interventions in neurological diseases.

Keywords: Alzheimer's disease, multiple sclerosis, ischemic brain stroke, subarachnoid hemorrhage, tyrosine kinases, tyrosine kinase inhibitors.

INTRODUCTION

Tyrosine kinase inhibitors (TKI) are well established targeted therapy of various types of malignancies. At present these agents are being widely investigated outside their designated field of use *i.e.* in non-oncology diseases, whose pathogenesis involves inflammatory and/or autoimmune processes.

Many reports have provided experimental evidence for efficacy of TKIs in several neurological and non-neurological disorders, including among others ischemic and hemorrhagic brain stroke [1, 2], Alzheimer's disease [3], multiple sclerosis [4], rheumatoid arthritis [5], asthma [6], mastocytosis [7] and other. Thus, TKIs may represent an innovative avenue for treatment of these diseases.

In this context, it is worth mentioning the current concept concerning the role of tyrosine kinase (TK) itself in the signaling transduction pathways. These enzymes are essential in numerous processes that control cellular proliferation and differentiation, regulate cell growth and its metabolism as well as promote cell survival and apoptosis. By targeting these enzymes TKIs modify the inflammatory and immunological responses, which seems to be the pathophysiological basis in the illnesses mentioned above.

All of the representatives of TKIs share the same mechanism of action, although they differ from each other in the spectrum of targeted kinases and substance-specific actions. They are commonly divided into two subgroups: receptor tyrosine kinase inhibitors (RTKI) and non-receptor kinase inhibitors (NRTKI). The members of the first one interact with ATP-binding sites of the receptor tyrosine kinases (*e.g.* growth factor receptors, c-kit, Flt-3, ephrin receptor, neurotrophin receptor and other), the members of the second one are also ATP-dependent, but structurally they possess a variable number of signaling domains, including a kinase one (Src family including *e.g.* Src, Fyn, Lyn, Lck and Abl family – Abl1, Abl2).

With respect to pharmacokinetics, TKIs, with the exception of small differences, show similarities in GI (gastro-intestinal) absorption, distribution, metabolism and elimination.

Generally, this review provides data on new non-oncological applications of TKIs however, limited to selected neurological disorders (ischemic brain stroke, subarachnoid hemorrhage, Alzheimer's disease, multiple sclerosis) with an attempt to indicate the possible mechanisms of the drug action in these pathological conditions.

TYROSINE KINASES: DEFINITION, CLASSIFICATION AND CONTRIBUTION IN PATHOGENESIS OF DISEASES

Tyrosine kinases catalysing the transfer of phosphate group from ATP to tyrosine residues in protein substrates are involved in the regulation of both physiological and pathological functions in many species, including human

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beings. There is a great number of different TKs and they are classified into two subgroups: receptor tyrosine kinases (RTK) and non-receptor tyrosine kinases (NRTK). Both of them catalyze the addition of phosphoryl group on a tyrosine residue, but at different locations within the cell – whereas receptor tyrosine kinases are transmembrane proteins, non-receptor tyrosine kinases are intracellular. All of the TKs are broadly distributed in the body however, some of them show specificity to a particular organ *e.g.* to the brain or even its area (EphA4 is highly expressed in the hippocampal tissue, while c-Abl in the temporal neocortex structures [8, 9].

There are 58 known RTKs in mammalian cells distributed into 20 families based on their structural characteristics, and the most important comprise growth factor receptors (EGFR, VEGFR, PDGFR, FGRF), c-kit, TrkB, Flt-3. These membrane-bound receptors are activated by growth factors, cytokines and hormones. A simplification of the sequence of events after activation of RTKs is as follows. It starts with ligand binding at the extracellular level which induces oligomerization of the receptor monomers, usually dimerization. Next, trans-phosphorylation of the tyrosine residues in the cytoplasm occurs, which enables their recognition by cytoplasmic proteins with SH2 or phosphotyrosine binding (PTB) domains. This in turn triggers different signaling cascades and the main activated by RTKs are: phoshoinositide 3-kinase (PI3K)/Akt (also known as protein kinase B), Ras/Raf/ERK1/2, STAT pathways. Intracellular mediators in these pathways transduce extracellular signals to the cytosol and into the nucleus and thereby there is a regulation and control of a variety of biological processes *e.g.* cell proliferation and differentiation, cell cycle control, cell survival. They are vital to cell biology including both physiological and pathological conditions. Over-expression of some RTKs is the main factor responsible for the development of different pathogenic processes. On the other hand, such phenomenon is relevant post-injury as it happens *e.g.* in different kinds of CNS insults. One of the pathways which becomes activated in these conditions is BDNF (brain derived neurotrophic factor)-TrkB-PI3K/Akt pathway bringing about improved brain plasticity, neuronal survival and long-term functional recovery [10-12].

The NRTKs include 32 cytoplasmic members classified into 10 families [13] with bcr-Abl and Src kinases of the utmost significance. Generally, the Abl family of protein kinase (Abl1, Abl2) links diverse extracellular stimuli to signaling pathways that control cell growth, survival, invasion, adhesion and migration [14]. Additionally, Abl1 may be involved in neutrophilin 1-induced angiogenesis, which proceeds in a VEGF-independent fashion [15].

Some family members of Src are ubiquitously expressed (*e.g.* Src, Fyn), while others are more tissue-specific (*e.g.* Lyn, Lck), including CNS. In the brain this family has miscellaneous physiologic and pathological roles, acting as a common signal mediator. In particular, it regulates the activity of NMDA receptor, which becomes activated *e.g.* during ischemic stroke. As a result, a large and prolonged Ca^{2+} influx into the neurons occurs, which culminates in cell damage [16-18]. Theoretically, Src family may be involved in a multitude of pathways of possible importance to ischemic brain pathology. Among them the well documented are those participating in cytokine release and superoxide production by neutrophils, and the signaling events in response to VEGF, which modulates vascular permeability and contributes to cerebral edema [16].

So far, the most evidenced role of TKs has been found in different kinds of cancers in which the enzymes are constitutively activated due to mutation or over-expression leading to unregulated cell proliferation. TKs have also been implicated in the development of diseases in which inflammatory and autoimmune processes are involved. They include among others brain ischemic and hemorrhagic stroke, Alzheimer's disease, multiple sclerosis.

TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors are divided into monoclonal antibodies and small molecule tyrosine kinase inhibitors (TKIs). The latter one may fall into three categories: 1) receptor tyrosine kinase inhibitors (RTKIs), 2) non-receptor tyrosine kinase inhibitors (NRTKIs) and 3) mixed tyrosine kinase inhibitors. The representatives of the first group are: gefitinib, erlotinib, lapatinib (the most selective for EGFR), sunitinib, pazopanib, masitinib, lestaurtinib, sorafenib; of the second group are: dasatinib, bosutinib (the targets are bcr-Abl, Src); of the last one are: imatinib and nilotinib (bcr-Abl, c-kit, PDGFR).

Although, the data concerning the presented here TKIs focus mainly on oncological usage, there are promising clinical trials with some of the representatives of this group in the treatment of neurological disorders. Generally, the action of the drugs will be dependent on the particular kinases they target. An additional layer of specificity will be linked with the function of the cells that express the transcript and protein. An over-expression of versatile tyrosine kinases is a characteristic feature for the neurological illnesses considered in this review.

ISCHEMIC BRAIN STROKE

Pathophysiology of ischemic stroke is complex and involves early and late phase processes such as apoptosis, neuroinflammation, BBB (blood brain barrier) breakdown, neurovascular repair and regeneration. Despite great improvement in the understanding of the histopathological and molecular background of brain damage during the early phase of acute stroke, still the preventive measures remain the most effective method of restricting mortality in this condition. They include appropriate treatment of hypertension and atrial fibrillation (main causes of acute brain ischemia) and patient's education. At first, ischemic type of stroke should be diagnosed, which is not always an easy task, and confirmed promptly.

Apart from the introduction of the ABC procedures for emergency states, as supporting respiratory and circulatory functions, it is crucial to start with the most important treatment for ischemic stroke *i.e.* with acute reperfusion therapy. As has been demonstrated in this state, only rt-PA (recombinant tissue plasminogen activator), antiplatelets and anticoagulants have the capability of diminishing significantly the area of brain injury. The benefit of

thrombolysis of the occluded vessels produced by rt-PA administered within the first hours of stroke (the time window for safe usage has been very recently lengthened from 3 to 4.5 hours) is probably dependent upon the early maintenance of the BBB integrity, which rescues the affected ischemic zone and improves the clinical outcome. However, this kind of therapy has not been satisfactory because of its limitations, such as short time of therapy initiation and serious adverse effects. Administration of rt-PA beyond this time window increases the risk of further deterioration of BBB, which may result from up-regulation of endogenous t-PA induced by ischemia itself [19]. As a consequence, this agent gains access to the perivascular tissue and interacts with the neurovascular unit (NVU), leading in extreme cases directly to symptomatic hemorrhage [4]. The hemorrhagic complications probably result from the actions of t-PA in the brain, in which plasminogen, as a principal substrate is not involved. There is evidence that in this case the drug targets a specific substrate within NVU as the platelet-derived growth factor-CC (PDGF-CC) - a member of PDGF family that binds to the PDGF-α receptors – localized on the perivascular end-feet astrocytes. Activation of PDGF-CC *via* t-PA leads to an increase in BBB permeability and ischemia-induced neuronal damage [20]. How exactly the activated PDGF-CC mediates BBB damage is still not clear. However, recent studies have shown that LRP (a low-density lipoprotein receptor-related protein) may play a role in this process [21, 22] .

The weak points of rt-PA therapy have been an incentive for further research on agents which would improve its pharmacological profile. Among them TKIs such as imatinib or masitinib turned out to be efficacious. Both drugs expand rt-PA time window (up to 5 hours) [23], reduce brain infarct volume [23, 1] and hemorrhagic complications [23] without loss of thrombolytic rt-PA activity.

This favorable outcome has been attributed to the blocking effect of TKIs on the up-regulated by rt-PA brain PDGF-CC–PGFR-α signaling pathway which contributes to the neuronal deleterious actions (BBB dysfunction [19], hemorrhagic infiltration [19] and inflammation [24]) of the fibrinolytic drug.

Since the beneficial effects of TKIs in ischemic brain stroke result from the action in the CNS, it is worth considering their pharmacokinetics, especially the route of administration and access to the brain tissues. The drugs, being small molecular compounds are well absorbed from the GI. However, they have a low CNS distribution in healthy individuals [25], despite their high lipophilicity which enables adequate BBB penetration. The low concentrations in the brain result from an active pumping out from the brain cells because TKIs are substrates for ABC-family transporters [26]. Nevertheless, the limited CNS exposure to these compounds does not exclude their presence in the brain under pathological conditions in which BBB loses its integrity. This may happen in various cerebral injuries, including those which occur during ischemic stroke.

The first experimental trials with TKIs in ischemic stroke involved the usage of imatinib (GLEEVEC), a drug with well established position in human oncology. Imatinib is a drug targeting multiple kinases. The multi-target specificity of the drug has brought about on the one hand, many clinical benefits (approval for CML- chronic myelocytic leukemia, CLL-chronic lymphocytic leukemia and GIST- gastrointestinal stromal tumors), on the other difficulties in determining the biochemical basis of its efficacy [27]. In cancer diseases its most significant targets have been to a certain extent recognized (bcr-Abl, c-kit, PDGF), while they remain still vague in the non-oncological settings considered here. Most of the data available on this new subject concentrates on PDGF-α. As has been already mentioned, inhibition of this kinase by imatinib have led to a set of events which counteracted stroke-induced BBB disintegration, and by this means improved its final outcome.

Besides, this drug is known for the inhibition of other RTKs, as for example Flt-3, c-fms, which are critical components of the neuroinflammatory processes. Imatinib by blocking of Flt-3 and c-fms reduces the amount of neurotoxic pro-inflammatory cytokines (IL-1β, TNF-α) and accumulation of macrophages, respectively. Both mechanisms are also of importance in the alleviation of inflammatory symptoms when the drug is used in ischemic stroke.

The consequences of imatinib's inhibition of non-receptor TKs as Abl have been well documented mainly in oncology, and they resulted in both therapeutic (*e.g.* CML) and adverse drug reactions including diarrhea, vomiting, neutropenia and cardiotoxicity [28]. The data concerning its inhibition in ischemic stroke is really scanty. To date, it has not been determined whether over-expression of Abl occurs in this pathological state. On the other hand, there is evidence that treatment with imatinib inhibits both physiological and pathological angiogenesis *via* Abl1, but in VEGF2-independent fashion [15].

It is interesting that first non-tyrosine kinase targets of imatinib have been identified *i.e.* NQO2, V-ATP-ase. The first one is a cytoplasmic flavoprotein that takes part in the cellular response to oxidative stress, and the second one is a vacuolar ATP-ase functioning as a proton pump [29]. Of course, their role in ischemic stroke is not known.

Masitinib (KINAVET-CA1; MASIVIERA) is a novel potent and selective TKI, which targets particularly wild-type and mutated c-kit receptor, but also PDGFR α/β and Lck/Lyn TK, as well as FGFR3 and FAK. In comparison with imatinib, the drug shows a much smaller activity against Abl, and this is due to its chemical structure. Masitinib which possesses a highly hydrophobic thiazole ring, as compared with the polar pyrimidine ring of imatinib, is unable to produce a strong hydrogen bond network to three co-crystallised water molecules around the DFG (Asp-Phe-Gly) motif of Abl [24, 30], as imatinib does. Masitinib's selectivity of action brings about a quite acceptable safety profile. As the experiments on animals have demonstrated, the adverse drug reactions include mainly those resulting from c-kit inhibition (diarrhea, vomiting, edema, neutropenia). It should be emphasized that masitinib does not cause evident Abl- or Src-related cardiotoxicity or genotoxicity.

At present, the clinical significance of masitinib is negligible. Recently, the drug has been granted in humans a designation for pancreatic cancer (orphan treatment) [31], multiple sclerosis (experimental therapy) [4] and Alzheimer's disease (phase 2 clinical trial) [3]. Furthermore, the drug has gained approval for the treatment of malignancies (recurrent or nonresectable grade II or III cutaneous mast cells tumors) in dogs [32].

Also, the data concerning its usage in experimental models of ischemic stroke is poor. In rats treated with masitinib alone or in combination with rt-PA, the drug reduces the area of post-stroke brain ischemia and potentiates the fibrinolytic therapy [1]. The principal mechanism responsible for the favorable aforementioned actions of masitinib is attributed to inhibition of PDGFR, similarly as it has been described earlier for imatinib. Additionally, the decrease in mast cell activity in- or outside the CNS inhibits neuroinflammatory cascade and activity of microglia in the brain tissue [1]. Thus, masitinib could be regarded as an appropriate neuroprotective agent for combination therapy with rt-PA to improve the final outcome of ischemic stroke intervention.

Bosutinib (BOSULIF) is a competitive Bcr-Abl TKI with an additional inhibitory effect on Src family kinases. Recently, the drug has been approved for the treatment of chronic CML in adult patients with resistance or intolerance to prior therapy [33].

The inhibitory effect of bosutinib on Src kinases has been the basis for undertaking research, the purpose of which was to check the possible involvement of this family of kinases in the pathogenesis of ischemic stroke. If so, the drug could also represent a novel kind of brain injury treatment. According to the experimental investigations performed on tMCAO (transient middle artery occlusion) and pMCAO (permanent middle artery occlusion) models in rodents, bosutinib as well as other Src inhibitors (so far not been registered) reduce the infarct volume and protect against neuronal impairment [18]. These advantageous effects are brought about among others by disrupting the Src signal step in VEGF-induced vascular leakage [18] which contribute to cerebral edema [16].

SUBARACHNOID HEMORRHAGE (SAH)

The subarachnoid hemmorrhage accounts for approximately 27% of all stroke-related years of potential life lost before the age of 65 [34]. The early stage of subarachnoid hemorrhage, manifested by intracranial bleeding between the pial and the arachnoid membranes, leads to an increase in intracranial pressure, disruption of BBB, edema formation, activation of inflammatory and apoptotic processes [35]. Next, delayed cerebral vasospasm (CVS) occurs due to prolonged contraction of vascular smooth muscles. Despite advances in diagnosis, almost half of the survivors suffers from long-term effects of stroke *i.e.* impaired cognitive, visuospastial, language and sensorimotor functions [36]. So far, the method of SAH treatment including surgical management or pharmacotherapy has not been satisfactory. Therefore, new therapeutic strategies are still being searched for. They focus on alleviating pathogenic processes attending in the early brain injury (EBI) and in the development of delayed cerebral vascular spasm.

Similarly as in the case of ischemic stroke, imatinib, due to inhibition of PDGF signaling, produces a therapeutic effect reflected by decreases in SAH-induced BBB disruption, edema formation and pathogenesis of CVS [37, 38]. Moreover, more detailed mechanisms resulting from PDGF inhibition have been ascribed to each of the therapeutic effects produced by the drug, as *e.g.* increase in BBB integrity, drop in edema formation - to inhibition of JNK/c-Jun-mediated MMP-9 (matrix metalloproteinase 9), and prevention of the occurrence of CVS - to normalization of the tenascin-C expression [37]. The benefits of imatinib treatment have also been attributed to its anti-inflammatory actions which included inhibition of leukocyte migration through the BBB and a broad reduction of cytokines and their receptors [37].

ALZHEIMER'S DISEASE (AD)

Alzheimer's disease is the most prevalent cause of age-related dementia. It is characterized clinically by cognitive loss in two or more domains, including memory, language, calculations, orientation and judgment. Cognitive deficits resulting from synaptic malfunction or synaptic loss are the first signs of AD which occur well before the development of disease-specific histopathology, manifested by appearance of senile plaques (extracellular amyloid β (Aβ) deposition) and neurofibrillary tangles [39].

According to the present opinion AD pathogenesis cannot be restricted to the neuronal compartment. An important role is also ascribed to immunological mechanisms in the brain in which participate astrocytes and microglia [40]. Activation of both types of glial cells (a distinctive feature of AD) by aggregated proteins triggers an immune response characterized by release of versatile inflammatory mediators which contribute to disease progression and severity. Microglia and astrocytes are arguably the major source of cytokines in Alzheimer's disease. Due to exposure to Aβ, they release cardinal pro-inflammatory interleukins (TNF α, interleukin 1 β), nitric oxide and other potentially cytotoxic molecules.

It is known, that numerous tyrosine kinases are expressed in microglia. Rodent and human findings provide evidence for an increase in active forms of non-receptor tyrosine kinases, Src and Lyn in reactive microglia [41, 42]. It is believed that Aβ serves as a specific stimulus for TK-based microglia activation leading to a pro-inflammatory phenotype of AD [42].

Apart from the pro-inflammatory action, Src family, being widely expressed in the mammalian CNS tissue, plays a versatile role in processes of brain cell proliferation and differentiation [43, 44] as well as synaptic plasticity, including learning and memory [45]. Among them a kinase of particular interest for AD is Fyn as it is involved in CNS myelination, synaptic function and placticity. It was found that Fyn pathway is relevant to linking Aβ–PrP^C (cellular prion protein being a high affinity binding site of Aβ) to NMDA receptor and *tau* dysfunction [46]. Over-expression

of Fyn in Alzheimer's disease enhances Aβ toxicity by dysregulation of NMDA receptor function, excitotoxicity and dendritic spine retraction [47].

The role of NRTKs in Alzheimer's disease is not confined to Src family, but it also comprises the Abl one, the presence of which has been identified in amyloid plaques, tangles and other sub-cellular locations. This kinase is assumed to carry out phosphorylation of *tau* protein and APP-intracellular domain (AICD) [48, 49]. By this means, Abl modulates AICD-dependent cellular responses, transcriptional induction as well as apoptosis, which could participate in the onset and progression of the neurodegenerative pathology of AD. There is compelling evidence for the neuronal Abl activity mediating microgliosis as well [42].

On the other hand, also activation of RTKs is implicated in AD. Among them c-kit and PDGFR signaling pathways are relevant. Modulation of microglial activity is ascribed to the former one, and stimulation of Aβ generation to the latter signaling pathway [42].

The role of tyrosine kinases in pathogenesis of Alzheimer's disease has been confirmed by the results obtained from the experimental trials with representatives of both groups of TKIs. The tested compounds are dasatinib (NRTKI) and masitinib (RTKI). Each of them attenuates amyloid-dependent microglosis [42, 3] however, different mechanisms participates in the achievement of the therapeutic effect. Dasatinib (SPRYCEL-approved for CML treatment) blockes Src and Lyn (relevant kinases for microgliosis) [41], and masitinib c-kit [3]. Additionally, a direct neuroprotective effect is attributed to dasatinib, as a result of Abl kinase inhibition [41].

Masitinib disrupting PDGF pathway possibly inhibits Aβ generation, and targeting Fyn or the Fak pathway - reduces damage caused by neurofibrillary tangles or Aβ protein [3]. The two latter kinases have been implicated in phosphorylation of *tau* protein and Aβ–induced cognitive impairment [50]. The beneficial effects masitinib have been further established in patients with mild to moderate Alzheimer's disease who participated in a randomised, placebo-controlled phase 2 trial [3]. Masitinib administered as an adjunct to standard treatments slowed the rate of cognitive decline as well as improved functional capacity of the patients [3]. These results have led to the launch of a large international phase 3 trial with this drug [51] which is still in progress.

MULTIPLE SCLEROSIS (MS)

Multiple sclerosis is an autoimmune disease of CNS characterized by neuroinflammation, oligodendrocyte depletion and destruction of the myelin sheath and axonal damage, which results in neurodegeneration and consequently in the formation of sclerotic plaques in the brain and spinal cord. These processes lead to an impairment of axonal conduction, and thereby to a development of a severe disability of the patients. Although, the precise mechanisms underlying MS remain still undefined, a pivotal role in pathogenesis of this illness is assigned to inappropriate or unregulated activation of the immune cells. The present treatment of MS is unsatisfactory because it targets only symptoms or non-selectively immune cells which culminate in serious side effects. Better understanding of the molecular processes engaged in the illness itself has provoked progress in new strategies directed more specifically toward immunological processes responsible for its pathogenesis. However, the ones which have been already developed are not efficacious enough as they reduce the number of exacerbations only in a small proportion of patients and are beneficial exclusively in relapsing-remitting forms of MS.

The search for new therapies has focused on TKIs because diverse TKs have been implicated in signaling of many immune cells [52], and therefore these kinases are important players in pathological processes characteristic for MS. Among them the most significant are c-Fms [53] and PDGFR [54] because they are involved in key aspects of MS pathogenesis.

The first of them, being a receptor for MCSF (macrophage colony-stimulating factor), becomes up-regulated in MS resulting in increased production of TNF, IL-1β and matrix metalloproteinases (MMPs) [55, 56]. The pro-inflammatory cytokines promote cell infiltration and inflammation [57], and the MMPs facilitate immune cell transmigration into the CNS by disruption of the BBB. Furthermore, these enzymes are responsible for degrading the myelin sheaths (fragmentation of myelin basic protein) and axon damage [58, 59]. Despite the described indirect effects, macrophages produce also demyelinization directly as they phagocyte myelin in brain lesions [60].

On the other hand, PDGFR activation of this pathway brings about an excessive proliferation of astrocytes which are involved in MS in several ways. Among others astrocytes contribute to astroglyosis and scar formation (inhibition of axonal regeneration and remyelination), production of pro-inflammatory cytokines and chemokines, glutamate homeostasis, breakdown of BBB (by producing MMPs) [61]. Other TKs of relevance in this demyelinating disease include: Lck (Abl pathway) [62], Flt-3 [63], c-kit [64], Lyn [4], Fyn [4], VEGFR [65].

Available research concerning preclinical MS therapy development, including TKIs, has been performed on EAE (experimental autoimmune encephalomyelitis) – a mouse model for MS, where the disease is induced in laboratory rodents by immunization with CNS-driven self-antigens. Although, EAE does not mimic exactly the mechanisms behind disease onset in humans, it is an extremely valuable and useful general model for studying the pathogenesis of MS and creating novel treatments [66, 67].

Considering TKIs, investigations concentrate mainly on drugs such as imatinib, masitinib, sunitinib (SUTENT), sorafenib (NEXAVAR) and lestaurtinib. By acting on the various cells of the immune system, they abrogate multiple aberrant TK signaling transduction pathways, leading to therapeutic efficacy. Among the drugs, imatinib is the one whose action on this experimental model has been mostly explored. This drug *via* distinct mechanisms could prevent EAE or mitigate its deleterious symptoms. Imatinib, by targeting Flt-3, c-kit, c-fms inhibits the production of pro-

Table.1. The application of TKIs in neurological disorders and their most important targets.

Potential Clinical Usage	TKI	The Most Important Targets	
		RTK	NRTK
Ischemic brain stroke	imatinib	PDGFRα, Flt-3, c-fms,	Abl
	masitinib	PDGFRα	
	bosutinib		Src family
SAH	imatinib	PDGFRα	
AD	dasatinib	PDGFR	Src family (Src, Lyn), Abl
	masitinib	PDGFR, c-kit	Fyn, Fak
MS	imatinib	Flt-3, c-kit, c-fms,PDGFR	Lck/Abl
	masitinib	PDGFR, c-kit	Lyn, Fyn
	sunitinib	PDGFR, c-kit, Flt-3, VEGFR	
	sorafenib	PDGFR, c-kit, VEGFR	
	lestaurtinib	Flt-3	

TKI= tyrosine kinase inhibitor; RTK= receptor tyrosine kinase; NRTK= non-receptor tyrosine kinase;

inflammatory cytokines (TNFα, IL-1β, IL-6) and by this means attenuates recruitment of inflammatory cells to the CNS. Moreover, the drug as an inhibitor of c-fms reduces MMP production and the direct detrimental actions of macrophages. Another benefit of imatinib usage in EAE could be taken from the inhibition of PDGFR which results in suppression of astrocyte proliferation and its pathological consequences (astroglyosis, scar formation, MMP – induced BBB break-down) [56].

Additionally, imatinib by blocking Lck/Abl signaling pathway inhibits T cells activation and release of IL-2, IL-7 and TNFγ. An extraordinary case-report concerns a patient with CML superimposed on missed MS treated with imatinib, in whom the drug ameliorated the neurological deficit. Improvement of the patient's condition was due to the drug's inhibitory action on CSF1 (macrophage-colony stimulating factor) and PDGFRs. Both TKs are up-regulated in the pathological cascade leading to MS [68].

PDGFR and c-kit are also the targets on which are acting masitinib, sorafenib and sunitinib. Inhibition of these kinases leads among others to a decrease in production of pro-inflammatory cytokines (c-kit) and in proliferation of astrocytes (PDGFR). Lestaurtinib (the last on the list) by targeted inhibition of Flt-3 kinase principally in dendritic cells attenuates CNS infiltration of pathogenic T cells and production of TNFα, IL-6, IL-23 [69]. This kinase is also inhibited by imatinib [70] and sunitinib [71]. On the other hand, sorafenib and sunitinib, are known for antagonizing VEGFR, which is implicated in focal BBB breakdown, inflammatory cells migration into the lesions and CNS plaque formation [72].

A confirmation of the therapeutic effect of TKIs has been also established in human beings. In a randomized pilot phase 2 clinical study in humans with progressive MS masitinib produced therapeutic benefits to PPMS (primary progressive MS) and rfSPMS patients (relapse-free subpopulations of PPMS). The principal culprits attacked by the drug are mast cells and dendritic cells, the activation of which in MS leads to neuronal damage (induction of astroglia to produce neurotoxic quantities of NO) and deregulation of T cell responses. The inhibitory action on c-kit, Lyn and Fyn activity is the plausible mechanism by which masitinib causes both the anti-inflammatory and immuno-modulatory effects [4]. At the end it is worth mentioning that the drug is relatively well tolerated by the patients [4].

CONCLUSIONS

1. TKs being richly expressed and widely distributed in tissues, including CNS, posses versatile biological functions (*e.g.* cell division and differentiation, cellular metabolism and growth). An up-regulated state of these kinases is a characteristic feature of the neurological disorders considered in this review (ischemic brain stroke, SAH, AD, MS). What is more, both types of tyrosine kinases (RTKs and NRTKs) are involved and play a key role in many aspects of the development and progression of these diseases.

2. TKIs produce a therapeutic effect in all of the described illnesses. The therapeutic efficacy irrespective of the disease brings about an alleviation of symptoms and a general improvement of the condition. The most beneficial actions of TKIs comprise an attenuation of neurodegenerative and inflammatory processes, as well as an increase in BBB integrity and homeostasis. So far, the efficacy of TKIs in these disorders has been demonstrated mainly on animal models. However, masitinib underwent with positive results the second phase of clinical trials in patients with Alzheimer's disease and MS [72].

3. The therapeutic potential of TKIs reflects their multi-target action. In Table **1** the potential clinical usage, the inhibitors and their targets (clinical useful for the particular disease) are summarized.

4. The provided evidence for efficacy of TKIs in neurological disorders seems to be promising for the future as it opens novel perspectives for treatment strategies of these severe diseases.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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