



Metalloproteinases and their inhibitors in neurological disease

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Abstract

Matrix metalloproteinases (MMPs) are a group of endopeptidases that degrade the extracellular matrix and are responsible for many physiological and pathological processes. We aim to review the MMP inhibition from a clinical perspective and its possible therapeutic use in the future. MMPs play a role in various neurodegenerative and cerebrovascular diseases such as large artery atherosclerosis and ischemic stroke; for example, MMPs increase blood–brain barrier permeability favoring neuroinflammation. Synthetic MMPs inhibitors have been tested mostly in oncological trials and failed to demonstrate efficacy; some of them were discontinued because of the severe adverse reactions. Tetracyclines, in submicrobial doses, act as an MMP inhibitor, although tetracyclines have not yet been proven effective in several neurological conditions in which they were tested against placebo; it is uncertain whether there may be a use for tetracyclines in cerebrovascular disease, as a neuroprotective agent or in dolichoectasia.

Keywords Cerebrovascular disease · Dilatative arteriopathy · MMP inhibition · Neurodegenerative diseases · Neuroprotection

Introduction

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases known for their capacity to proteolyze elements of the extracellular matrix (ECM), such as collagen, proteoglycans, laminin, elastin, and fibronectin (Allan et al. 1995). ECM comprises up to 20% of the brain volume (Nicholson and Rice 1986) and is an essential part of the central nervous system (CNS) (Rosenberg 2017). There are three principal compartments of the brain ECM: the basal lamina, the perineuronal nets, and the neural interstitial matrix (Lau et al. 2013). The basal lamina acts as a boundary between endothelial cells and CNS parenchyma (Lau et al. 2013) and is one of the major sites of action of the MMPs (Rosenberg 2017). The MMPs also act at the cell surface, activating growth factors, death receptors, and other signaling molecules (Rosenberg 2009).

There are at least 26 MMPs (Adhikari et al. 2017) divided into collagenases, gelatinases, stromelysins, and membrane-type MMPs (Rosenberg 2009). Collagenases degrade collagen, the main component of bone and cartilage, gelatinases degrade molecules in the basal lamina around capillaries to facilitate angiogenesis and neurogenesis, and stromelysins (MMP-3, MMP-10, MMP-11, and MMP-7) degrade components of the ECM. Membrane-type MMPs play a role in the activation of other proteases and growth factors (Rosenberg 2009). Matrilysin (MMP-7) degrades ECM elements such as collagen and laminin (Fanjul-Fernández et al. 2010).

MMPs are regulated at several levels, and one of these includes secreted proteins called tissue inhibitors of metalloproteinases (TIMPs) (Mastroianni and Liuzzi 2007). TIMPs are small glycoproteins that bind to MMPs, forming non-covalent complexes. These complexes inhibit the activity of the MMPs (Mastroianni and Liuzzi 2007; Castro et al. 2011). Four TIMPs have been described (TIMP-1, TIMP-2, TIMP-3, and TIMP-4). TIMPs are not specific, but they show some preference; i.e., TIMP-1 mainly inhibits MMP-9, whereas TIMP-2 inhibits MMP-2, etc. (Mastroianni and Liuzzi 2007; Castro et al. 2011; Rosenberg 2009). Under physiological conditions, there is a balance between MMPs and TIMPs. Inappropriate production of MMPs and/or TIMPs may lead to pathological

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conditions such as inflammation, disrupt wound healing, or promote invasion of cancer cells or contiguous spreading of infectious diseases (Mastroianni and Liuzzi 2007; Gutierrez et al. 2016). While MMPs are present in pathological processes such as neuroinflammation, they also play an important role in angiogenesis, bone growth, wound healing, and tissue regeneration (Mignatti and Rifkin 1996; Jabłońska-Trypuć et al. 2016).

The MMPs that most relate to brain processes are MMP-2, MMP-3, MMP-9, MMP-10, and MMP-14 (Rosenberg 2009). In the CNS, MMPs are absent or present in undetectable concentrations (Behl et al. 2021). MMP-2 is also present in healthy brain and in cerebrospinal fluid (Rosenberg 2009). MMP-3 is essential for neuroplasticity and neuroregeneration (Lech et al. 2019).

In pathological conditions, MMPs may cause increased blood–brain barrier (BBB) permeability by acting on the basal lamina and tight junctions in endothelial cells, resulting in the final common pathway of acute neuroinflammatory damage (Rosenberg 2009, 2017). MMPs are also involved in neuronal death, hypoxia/ischemia lesions, and demyelination (Behl et al. 2021; Rosenberg 2009) (Table 1).

In hypoxic-ischemic lesions, MMP-2, MMP-3, and MMP-9 increase the permeability of the blood–brain barrier with a consequent greater risk of hemorrhagic transformation (Rosenberg 2009).

Synthetic MMPs inhibitors have been created, and their study has been primarily in oncological clinical studies. However, all showed neutral or even negative results. One of the biggest problems and concerns is adverse reactions, as MMPs are also essential for cell function.

In addition to their antimicrobial effect, tetracyclines are potent inhibitors of MMPs due to their antiapoptotic activity, among other functions (Griffin et al. 2010; Jabłońska-Trypuć et al. 2016).

Methodology

We performed a search in PubMed with the following MeSH terms: “Matrix Metalloproteinase Inhibitors,” “stroke,” “dementia,” “intracranial aneurysm,” “aortic aneurysm,” “multiple sclerosis,” “clinical study,” “randomized controlled trial,” and “humans.”

Pharmacology

During the last decades, pharmaceutical companies have developed several synthetic MMP inhibitors (Tables 2 and 3). Due to the lack of efficacy or serious adverse effects, these drugs have been withdrawn in phase II or III studies. Only doxycycline has FDA approval for periodontitis.

Minocycline, a second-generation tetracycline, readily crosses the blood–brain barrier (Macdonald et al. 1973) and has neuroinflammatory and antiapoptotic actions, decreasing microglial activity and inhibiting the activity of MMPs so that it could play a role in the prevention of cell death (Stirling et al. 2005; Cankaya et al. 2019).

Because of the ability of tetracyclines to inhibit collagenolysis and angiogenesis, they have been used in an attempt to correct excessive collagen breakdown and possibly impact favorably early stages of the inflammatory cascade (Rosenberg 2009). Nonetheless, the use of MMP inhibitors has been associated with adverse side effects, and there is a theoretical concern that broad-spectrum MMP inhibitors that may block important functions such as remodeling the ECM may cause joint stiffness that limits their use (Rosenberg 2009). Photosensitivity and hyperpigmentation have also been described with broad-spectrum MMP inhibitors (Nakasujja et al. 2013; Frenzel et al. 2008). In a study comparing minocycline vs placebo in patients with HIV-associated cognitive impairment, 4% of the patients taking minocycline developed grade 2 hyperpigmentation, and 5% of the patients developed a grade 4 rash (Nakasujja et al. 2013). Furthermore, in a study with minocycline in AD, of

Table 1 Role of metalloproteinases in different neurological diseases

| Disease | Matrix metalloproteinase involved | Function |
|--------------------|-----------------------------------|--|
| Multiple sclerosis | MMP-9 | Demyelination and breakdown of the BBB (Gijbels et al. 1992) |
| Alzheimer disease | MMP-2, -9 | Contributes to A β -induced neuronal cell death (Wang et al. 2014) CSF levels of MMP-9 are elevated in persons with AD (Bjerke et al. 2011) |
| Huntington disease | MMP-10 | Inhibition of MMP-10 cleaves huntingtin and reduce cell death (Miller et al. 2010) |
| Parkinson disease | MMP-3 MMP-9 | Microglial activation, which contributes to degeneration neurons in Parkinson disease (Choi et al. 2008) Present in astrocytes and microglia, playing an important role in neuroinflammation in PD (Behl et al. 2021) |
| Dolichoectasia | MMP-9 | Large artery remodeling and associated with inflammation and dolichoectasia (Gutierrez et al. 2016) |

Table 2 Characteristics of different tetracyclines used as MMP inhibitors

| | Tetracycline | Minocycline | Doxycycline |
|------------------------------------|---|---|---------------------------|
| Spectrum MMP inhibition and effect | MMP-1, -8, -9, -13 More potent MMP-9 inhibitor than doxycycline ^a | Most potent MMP-9 inhibitor of all tetracyclines, very lipophilic (crosses more easily the BBB than other tetracyclines) ^b Reduce BBB damage ^c | Most potent MMP inhibitor |
| Adverse reactions | GI adverse effects | Liver toxicity, serum sickness and SLE CNS: benign intracranial hypertension | GI adverse effects |

^aModheji M, Olapour S, Khodayar MJ, Jalili A, Yaghooti H. Minocycline is More Potent Than Tetracycline and Doxycycline in Inhibiting MMP-9 in Vitro. *Jundishapur J Nat Pharm Prod.* 2016;11(2):e27377

^bMacdonald H, Kelly RG, Allen ES, Noble JF, Kanegis LA. Pharmacokinetic studies on minocycline in man. *Clin Pharmacol Ther.* 1973;14(5):852–861

^cRosenberg GA, Estrada EY, Mobashery S. Effect of synthetic matrix metalloproteinase inhibitors on lipopolysaccharide-induced blood–brain barrier opening in rodents: Differences in response based on strains and solvents. *Brain Research.* 2007;1133:186–192

those randomized to 400 mg or 200 mg minocycline daily, only 29% and 72% of participants completed the study, respectively. The reasons for discontinuing the treatment were dizziness and gastrointestinal and dermatologic adverse effects (Howard et al. 2020).

Cerebrovascular disease and related disorders

Acute ischemic stroke

MMP activation leads to BBB disruption (Rosenberg 2009). Some meta-analyses have shown that MMP-9 (–1562 C/T) gene polymorphism is associated with the risk of acute ischemic stroke (AIS) (Misra et al. 2018; He et al. 2017), as well as MMP-12 (–1082 A/G) gene polymorphism.

This association between MMP-9 (1562 C/T) gene polymorphism seems to be more marked in the Asian population (Jiang et al. 2020; Misra et al. 2018).

There is evidence too that that serum levels of MMP-8 and myeloperoxidase (MPO acts as an activator of MMP-8 (Saari et al. 1990)) are higher in patients with AIS than in controls (Palm et al. 2018). Furthermore, MMP-8 serum levels are lower in strokes due to small vessel disease compared to strokes due to cardioembolism or large vessel disease, although this difference may relate to variations in stroke size (Palm et al. 2018).

Because MMPs disrupt the BBB, MMP inhibition has been investigated as a therapeutic intervention in AIS. In rats with occlusion of the middle cerebral artery, treatment with minocycline showed a significant decrease in the expression of MMP-2 and MMP-9 in the brain compared to controls. Importantly, this study also demonstrated that the MMP inhibitory effect of minocycline did not affect the fibrinolytic activity of intravenous tissue plasminogen activator (tPA) (Machado et al. 2009). However, MMP inhibition

with BB-1101 (a broad-spectrum MMP inhibitor) did not reduce the infarct size in rats after 48 h, and in fact, it led to neurological deterioration (Sood et al. 2008).

Three RCTs compared minocycline 200 mg versus placebo for 5 days orally administered in patients with an AIS with onset between 6 and 24 h. The three studies showed a lower National Institutes of Health Stroke Scale (NIHSS) at 90 days after randomization (Padma Srivastava et al. 2012; Lampl et al. 2007; Amiri-Nikpour et al. 2015). Additionally, in two of these studies, the Barthel Index was higher, and the modified Rankin Score (mRS) was lower in the minocycline group (Padma Srivastava et al. 2012; Lampl et al. 2007). No differences were seen in hemorrhagic transformation, recurrent stroke, or myocardial infarct (Padma Srivastava et al. 2012; Lampl et al. 2007). Interestingly, a subgroup analysis by sex showed that NIHSS was lower in men who received minocycline compared with women (Amiri-Nikpour et al. 2015). Despite this early success, not all studies have reproduced the beneficial effect of MMP inhibition in the acute stroke setting. Another study using minocycline 100 mg administered intravenously within 24 h of stroke onset versus placebo did not show efficacy in terms of functional independence at day 90 (Kohler et al. 2013). A meta-analysis of seven RCTs (including the four mentioned above plus two including hemorrhagic strokes and one including both ischemic and hemorrhagic strokes) using minocycline versus placebo confirmed that minocycline was associated with greater functional independence and motor performance (measured by mRS, Barthel Index, and NIHSS) compared to placebo in patients with AIS, but not in patients with hemorrhagic stroke (Malhotra et al. 2018). Larger studies are needed to verify the effectiveness of minocycline in the management of AIS, especially in combination with mechanical thrombectomy.

MMPs play a role in all stages of atherosclerotic disease. In brain larger arteries with advanced atherosclerotic disease, MMPs promote plaque rupture (Fig. 1) (Huang et al.

Table 3 Properties of broad-spectrum and selective MMP inhibitors used in previous clinical trials

| MMP inhibitor | Spectrum MMP inhibition | Disadvantages Adverse effects |
|--|---|--|
| Batimastat (BB-94) | Broad spectrum | Poorly oral bioavailability (necessary intraperitoneal administration) ^a Fever, elevation of liver enzymes, peritoneal irritation, abdominal pain, diarrhea, headaches |
| Marimastat | Broad spectrum | Toxicity of GI tract, weight loss, inflammation, fibrosis, hemorrhage, necrosis of tissue, musculoskeletal syndrome Lack of efficacy in trials ^a |
| GI129471 | Inhibition of MMP-2 ^b TNF-alfa ^c | Simultaneously increase MMP-9 |
| Tanomastat BAY-12-9566 | MMP-2,-3,-8,-9, -13 ^d | Inferior survival in pancreatic cancer trial and small cell lung cancer ⁴ Elevated transaminases, thrombocytopenia Canceled |
| Ilomastat | MMP-2, cardioprotector | Poor bioavailability ^e |
| Neovastat AE-941 (shark cartilage derivate) | Anti-metastasis and anti-angiogenic effects by inhibiting vascular endothelial growth factor and MMPs | No statistically significant difference in overall survival in oncologic trials ^f Taste alteration ^g |
| D-5410 | Broad spectrum | Poor bioavailability ^a |
| CGS-27023A (MMI-270) | Broad spectrum Inhibits MMP-1, MMP-2, MMP-9, and MMP-13 | Lack of efficacy and severe toxicities ^a Joint and Muscle pain, skin rash ^a Canceled in Phase I clinical trial ^d |
| Prinomastat AG-3340 | Orally and peritoneal MMP-2, MMP-3, MPP-9, MMP-13 | Lack of efficacy in clinical trials Severe toxicity Arthralgia, stiffness and joint swelling ^h |
| Rebimastat | MMP-1, -2, -3, -8, -9, -13, and 14 | Lack of efficacy in cancer trials General toxicities, arthralgia |

^aPeterson JT. Matrix metalloproteinase inhibitor development and the remodeling of drug discovery. *Heart Fail Rev.* 2004;9(1):63–79

^bMaquoi E, Munaut C, Colige A, et al. Stimulation of matrix metalloproteinase-9 expression in human fibrosarcoma cells by synthetic matrix metalloproteinase inhibitors. *Exp Cell Res.* 2002;275(1):110–121

^cMurakami K, Kobayashi F, Ikegawa R, et al. Metalloproteinase inhibitor prevents hepatic injury in endotoxemic mice. *European Journal of Pharmacology.* 1998;341(1):105–110

^dCathcart JM, Cao J. MMP Inhibitors: Past, present and future. *Front Biosci (Landmark Ed).* 2015;20:1164–1178

^eMillar AW, Brown PD, Moore J, et al. Results of single and repeat dose studies of the oral matrix metalloproteinase inhibitor marimastat in healthy male volunteers. *Br J Clin Pharmacol.* 1998;45(1):21–26

^fLu C, Lee JJ, Komaki R, et al. Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial. *J Natl Cancer Inst.* 2010;102(12):859–865

^gBatist G, Patenaude F, Champagne P, et al. Neovastat (AE-941) in refractory renal cell carcinoma patients: report of a phase II trial with two dose levels. *Ann Oncol.* 2002;13(8):1259–1263

^hBecker DP, Barta TE, Bedell LJ, et al. Orally Active MMP-1 Sparing α -Tetrahydropyryl and α -Piperidinyl Sulfone Matrix Metalloproteinase (MMP) Inhibitors with Efficacy in Cancer, Arthritis, and Cardiovascular Disease. *Journal of Medicinal Chemistry.* 2010;53(18):6653–6680

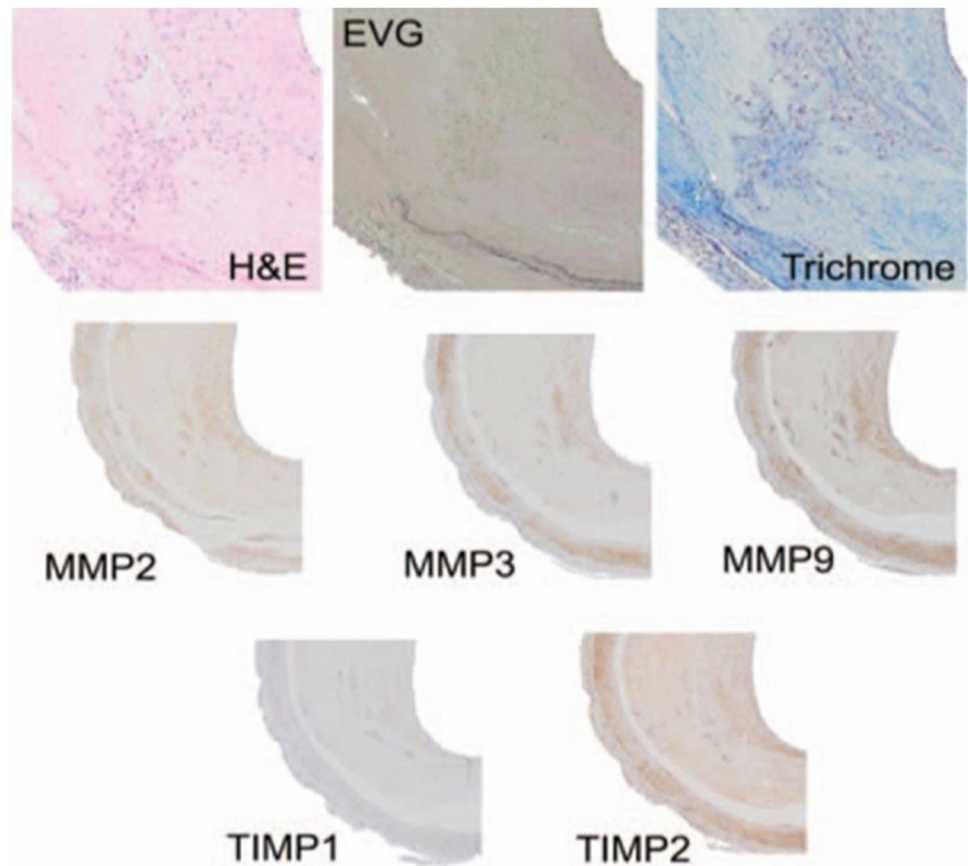
2017; Hunter et al. 2018; Myasoedova et al. 2018). A study of autopsied cerebral arteries in HIV + patients versus HIV-negative controls found a greater imbalance of MMPs and TIMPs (greater staining of MMP-2, MMP-3, and MMP-9 as well as less staining of TIMP-1 and TIMP-2) in HIV-positive patients and with a cell count of < 200 cel/ul. This imbalance suggests a greater elastolytic activity, which suggests greater vulnerability of the plaques to endothelial injury and thrombosis, which could lead to a higher incidence of AIS in patients with HIV (Hunter et al. 2018). A future therapeutic option may be to consider MMP inhibition in vulnerable or high-risk plaques to stabilize the plaque and

decrease the short-term risk of artery-to-artery embolism or in situ thrombosis. It is of interest to know if the inhibition of MMPs by tetracyclines would have an effect on hemorrhagic transformation after an AIS.

Vascular dementia

Patients with multi-infarct dementia or dementia in the setting of small vessel disease have higher CSF concentrations of MMP-9 compared with non-demented controls or with patients with Alzheimer's dementia (Adair et al. 2004). Another study showed increased levels of MMP-10 in CSF

Fig. 1 Higher intensity staining for MMP-2, MMP-3, and MMP-9 with weaker staining for TIMP-1 and TIMP-2 on the intima layer demonstrating that MMPs are involved in plaque growth and rupture



in patients with subcortical vascular disease and patients with Alzheimer's dementia compared to controls (Bjerke et al. 2011). Similarly, high brain MMP-3 (Rosenberg et al. 2001) but decreased plasma levels of TIMP-1 (Lorenzl et al. 2008) has been associated with vascular dementia compared to controls. Whether MMP regulation may be a therapeutic target for vascular dementia remains unclear.

Dilatative arteriopathies

Dolichoectasia

Dolichoectasia is a common cause of stroke and carries a high risk of mortality (Gutierrez et al. 2011). In a study of autopsied brains, our group demonstrated that large artery dolichoectasia was associated with higher MMP-9 and MMP-2 expression and lower TIMP-2 (Gutierrez et al. 2016). In another study, levels of serum MMP-2 were higher in the presence of a cervical carotid kink or tortuosity than in their absence (Arslan et al. 2016). Nonetheless, in another study, intracranial dolichoectasia was associated with lower serum levels of MMP-3, but not MMP-2 or MMP-9 (Pico et al. 2010). In this study, there

was a negative correlation between basilar artery diameter and MMP-3 serum levels. It is unknown whether MMP-modifying therapies may play a role in dolichoectasia.

Intracranial saccular aneurysms

Inflammation plays a role in aneurysm formation and rupture. Inflammation leads to a release of MMPs that degrade and remodel the ECM (Hashimoto et al. 2005). ECM degradation leads to weakness of the vessel wall and rupture (Hashimoto et al. 2005). A feasibility study in patients with brain arteriovenous malformations or intracranial aneurysms randomized participants to doxycycline or minocycline (200 mg/day) up to 2 years; only 10 of 26 patients completed the 2 years of treatment. Treatment-related adverse events occurred in 13 of 26 patients. The minocycline group tended to have more side effects, but no statistically significant (Frenzel et al. 2008). Although the authors recommended a more comprehensive study to assess the risk of bleeding in cerebral vascular malformations with minocycline or doxycycline, no more clinical trials are known. Further RCTs are required to confirm the findings of this preliminary study.

Abdominal aortic aneurysm (AAA)

MMP inhibition has been tested among people with AAA and may inform of possible therapeutic role for MMP inhibition in brain dilatative arteriopathies. For example, doxycycline is safe in patients and reduces the growth rates of abdominal aortic aneurysms (Baxter et al. 2002) and, when administered for 2 weeks, alters aortic wall neutrophil and cytotoxic T cells content in patients undergoing elective AAA repair (Lindeman et al. 2009). In patients randomized to doxycycline 100 mg twice daily or placebo for 6 months after endovascular aneurysm repair showed that participants who received doxycycline had lower MMP-9 plasma levels at 6 months compared to baseline. However, there was no significant effect of doxycycline in aneurysm size (Hackmann et al. 2008). Furthermore, another study of small AAAs in which participants were randomized to doxycycline 100 mg versus placebo for 18 months was stopped early because an interim analysis showed an unexpected increase in aneurysm growth in the doxycycline group (Meijer et al. 2013). Similarly, another RCT of 254 patients investigated doxycycline 100 mg twice daily for 24 months aimed at growth reduction of small AAAs. At the 24-month follow-up mark, doxycycline did not significantly reduce the aneurysm growth (Baxter et al. 2020). The maximum transverse diameter (mean change) after 2 years was 0.36 cm in both groups.

Neurodegenerative disorders

Alzheimer's disease

There is evidence that MMPs play a role in [Alzheimer's disease](#) (AD). MMP-9 is elevated in persons with AD, and TIMP-1 and MMP-9 have been proposed as CSF-markers, in addition to T-Tau, P-Tau₁₈₁, and A β ₁₋₄₂ (Bjerke et al. 2011). It has been shown that MMP-14 is negatively correlated with amyloid precursor protein expression in the hippocampus of persons with AZ (Cheng et al. 2018).

Because tetracyclines have an *in vitro* anti-amyloidogenic activity inhibiting the formation of β -amyloid aggregates (Forloni et al. 2001), there have been studies focusing on MMP inhibition in AD. A multicenter RCT explored if 24-month treatment with 200 mg or 400 mg minocycline vs placebo could modify cognitive and functional decline in patients with mild AD. There were a considerable number of treatment withdrawals; however, the treatment with minocycline did not show any significant difference in delaying the progress of cognitive or functional impairment (Howard

et al. 2020). In a pilot study, 101 individuals with mild AD were randomized to orally intake of doxycycline 200 mg daily plus rifampin 300 mg daily for 3 months or to placebo. The outcome was defined as a change in the standardized Alzheimer's Disease Assessment Scale-cognitive subscale (ADAScog) at 6 and 12 months. There was significantly less worsening in the ADAScog at 6 months in the doxycycline/rifampin group but no significant differences at 12 months, however (Loeb et al. 2004). Another multicenter RCT of individuals with mild to moderate AD randomized 406 participants to four groups: doxycycline 100 mg twice daily plus rifampin 300 mg daily, doxycycline 100 mg twice daily plus placebo, rifampin 300 mg plus placebo, and placebo-doxycycline plus placebo-rifampin. The study failed to demonstrate the benefit of doxycycline with or without rifampin (Molloy et al. 2013). It is uncertain whether risk stratification among people with AD and evidence of dysregulated MMPs may respond better to doxycycline.

Huntington's disease

Huntington's disease (HD) is an autosomal neurodegenerative disorder characterized by a progressive movement disorder associated with psychiatric and cognitive decline. It has been shown that MMP-10 cleaves huntingtin, and decrease of MMP-10 reduces cell death in HD (Miller et al. 2010). Studies in mice showed a beneficial effect of minocycline delaying progression disease (Stack et al. 2006). A pilot study with 14 patients with genetically confirmed HD received minocycline 100 mg daily for 24 months. After 1 year, three patients were lost to follow-up, and 11 patients were psychiatrically, neurologically, and neuropsychologically evaluated. In the remaining 11 participants, neurological, neuropsychological, and psychiatric scoring remained stable or improved, but the motor symptoms did not improve (Bonelli et al. 2004). Subsequently, the Huntington Study Group-DOMINO conducted an RCT using a futility design. The null hypothesis was that minocycline would reduce the mean decline in the Total Functional Capacity (TFC) Score from baseline to 18 months by at least 25% compared to placebo and a historical database from past clinical trials in HD. One hundred fourteen participants were randomized to minocycline 100 mg twice daily or placebo. Mean TFC Score decline in the minocycline group was greater than the pre-specified 25% but not statistically significant (Investigators, The Huntington Study Group DOMINO 2010). Investigators concluded that it would be futile to proceed with another clinical trial using minocycline involving more participants.

Creutzfeldt-Jakob disease

A phase 2 RCT tested the efficacy and safety of doxycycline 100 mg daily in the treatment of Creutzfeldt-Jakob disease (CJD). The primary outcome was survival from the time of randomization to death. After an interim analysis of 121 patients, the trial was stopped because of the lack of superiority of doxycycline compared with placebo (Haik et al. 2014). Another study explored the use of doxycycline 100 mg. The study consisted of two parts. In the first part, a double-blinded RCT, seven participants in early stages of CJD in the treatment group vs five controls with placebo were enrolled. The median survival time was greater in the doxycycline group versus controls (95 vs 33 days) but not statistically significant (HR 0.481, 95% CI 0.238–2.966) (Varges et al. 2017). The second part was an observational study with patients who were treated compassionately with doxycycline vs a matched treatment-naive control and showed a modest although statistically significant increase in survival time (unadjusted median survival time for doxycycline group was 346 days versus 208 days for the control group, HR 0.607, 95% CI 0.372–0.989). The results of both studies were combined and showed a slight increase in survival time in the doxycycline group ($p=0.049$, HR 0.63, 95% CI 0.402–0.999) (Varges et al. 2017). More clinical trials in early-stage CJD are needed to define whether MMP inhibition should be routinely recommended in people with CJD.

Parkinson's disease

MMP-3 is involved in microglia activation, thus playing an important role in neuronal degeneration in [Parkinson's disease](#) (Choi et al. 2008).

As a potent inhibitor of microglial activation, minocycline was used in a phase 2 clinical trial to test the safety and progression of the disease in patients with a recent diagnosis of Parkinson's disease that did not yet require symptomatic treatment. Participants were randomized to placebo, creatine (nutritional supplement), or minocycline (200 mg/day). Although minocycline was not declared futile, no reduction in disease progression was shown (Ninds Net-Pd Investigators 2006). An extension of the study with a follow-up in an additional 6 months (18 months in total) also showed no effect on the progression of Parkinson's disease (Ninds Net-Pd Investigators 2008). Authors recommended a larger phase 3 study.

Neuroimmunology

Multiple sclerosis

Exacerbation of acute multiple sclerosis (MS) causes an increase in MMP-9 concentrations in CSF (Gijbels et al.

1992). Treatment with high-dose prednisolone, which restores BBB integrity, lowers MMP concentrations in CSF (Rosenberg et al. 1996). Furthermore, minocycline reduces the gadolinium-enhancing lesions in MRI (Metz et al. 2004). Two studies tested minocycline 100 mg twice daily for 6 months and doxycycline for 4 months, respectively, in patients with relapsing–remitting MS. Both studies showed a reduction in contrast-enhancing lesions on MRI (Zabad et al. 2007; Minaagar et al. 2008). Another pilot study evaluated minocycline 100 mg twice daily in 10 patients with relapsing–remitting MS for 36 months and found a reduction in the mean total number of contrast-enhanced lesions during the first 6 months of treatment compared with the 3 months run-in period (0.22 vs 1.38); the mean total number of contrast-enhanced lesions dropped until 0.09 during the last 30 months treatment extension (Zhang et al. 2008). Another study compared glatiramer acetate plus minocycline versus glatiramer acetate plus placebo in 44 relapsing–remitting MS patients for a total of 9 months and showed a trend toward greater reduction in the total number of contrast-enhancing lesions on T1-weighted images and the number of confirmed relapses (Metz et al. 2009). Another RCT combined interferon- β -1a with minocycline 100 mg twice daily vs interferon- β -1a with placebo for 96 weeks in relapsing–remitting MS, 149 patients were randomized to the intervention group, and the primary efficacy endpoint (time to first qualifying relapse) was similar for both groups, showing that minocycline added to interferon- β -1a had no significant benefit (Sørensen et al. 2016).

HIV-associated neurocognitive disorders

Human immunodeficiency virus (HIV) affects directly the CNS and causes various neurological syndromes, including HIV-associated neurocognitive disorders (HAND) (McArthur et al. 2010). MMP-1 and MMP-9 are increased during primary HIV infection, and imbalance between MMPs and TIMPs contributes to progression of HIV-associated disorders (Mastroianni and Liuzzi 2007). Minocycline is a potent inhibitor of gelatinases (Paemen et al. 1996) and has been tested in human and animal HIV models of HAND. In an animal study, pigtailed macaques were intravenously inoculated with simian immunodeficiency virus; five of them were treated with minocycline (4 mg/kg per day), and six received no treatment. The macaques were sacrificed on day 84. In the untreated macaques, three developed moderate encephalitis, two severe, and one developed no encephalitis; in the group treated with minocycline, three out of five macaques did not develop encephalitis, and the other two macaques developed only mild encephalitis (Zink et al. 2005). Furthermore, minocycline suppressed viral load in the brain and decreased the expression of CNS inflammatory markers. In another study in humans, 107 HIV+ individuals on antiretrovirals with cognitive impairment received

either minocycline 100 mg or placebo orally twice daily for 24 weeks. A baseline neuropsychological test was performed and at 12 and 24 weeks. In the primary analysis, the study did not show a benefit of minocycline on HAND (Sacktor et al. 2011). As a secondary analysis, CSF of 21 individuals out of 107 included (13 of the placebo group and 8 of minocycline group) was studied for markers of oxidative stress, neuronal injury, and inflammation. In the minocycline group, there was a reduction in ceramides (indicator of oxidative stress); however, there were no statistically significant changes in protein carbonyl, CSF neurofilament heavy chain, neurotransmitters, or markers of inflammation such as tumor necrosis factor alpha, interleukin-6, interleukin-8, and hepatocyte growth factor (Sacktor et al. 2014). A second RCT in Uganda enrolled 73 people with HIV (90% women) not on antiretrovirals to test whether minocycline had an effect on neurocognitive performance. In this study, minocycline failed to demonstrate a benefit in neurocognitive performance and provided class II evidence that minocycline 100 mg twice a day for 24 weeks does not improve HAND (Nakasujja et al. 2013).

Conclusions

Broad-spectrum and selective MMP inhibitors have been studied as therapeutic strategies in neurological and vascular conditions, but the record of effectiveness and safety is mixed. Adverse effects to MMP inhibitors are time-dependent, mostly seen in medium- and long-term clinical trials. Based on this, a more promising option may be to focus on short-term MMP inhibition. Such scenario may include AIS in which short-term MMP inhibition is hypothesized to prevent BBB disruption and vasogenic edema, therefore reducing the risk of hemorrhagic transformation or stabilizing vulnerable atherosclerotic plaques prone to rupture. In cases of intracranial dolichoectasia, MMP inhibition should be further studied, given the poor prognosis and lack of alternative specific treatments. Tetracyclines are well-known and cost-effective drugs, and their use could be easily implemented in clinical practice if proven effective in RCT.

Expert opinion

Tetracyclines are MMP inhibitors that have been studied for several decades and have not yet reached a primary clinical application as MMP inhibitors. In cerebrovascular disease, specifically in ischemic stroke, a positive trend has been seen in terms of functional status at 90 days post-stroke with the use of tetracyclines, but further

replication of these results is needed. MMP inhibition has been explored as a neuroprotection strategy in people with ischemic stroke, but no significant results have been achieved. Because these trials were conducted before the thrombectomy era, it would be reasonable to reevaluate whether tetracyclines may play a role as neuroprotective therapies in conjunction with mechanical thrombectomy and thrombolysis.

Dilatative arteriopathy is a disease without specific treatment and with devastating consequences. Increased MMP expression in the arterial wall has been postulated to be a driving force in the progression of this disease. Therefore, MMP inhibition with tetracyclines or other specific compounds could be a plausible therapeutic target to be studied. The use of tetracyclines in other arteriopathies such as saccular aneurysms or arteriovenous malformations remains uncertain.

There is promising data regarding MMP inhibitors' use for patients with Creutzfeldt-Jakob disease, as doxycycline relates to discreet survival benefits. Further studies using MMP inhibition in earlier stages of the disease are advisable.

One point of concern is the tolerability of tetracyclines and their adverse effects. Gastrointestinal effects are common and lead to poor compliance. Synthetic MMP inhibitors have also been associated with carcinogenicity. We believe that shorter exposures to MMP inhibitors may be able to overcome these side effects associated with chronic use.

Although the track record of MMP inhibition as a therapeutic modality has mixed results and only a few clinical indications, several ongoing trials are studying the use of MMP inhibition or modification in various conditions (as of May 2021, 96 protocols related to "metalloproteinases" were listed as active in clinicaltrials.gov) (see Table 3). In neurology, some studies include minocycline as a neuroprotective agent in AIS or to decrease the risk of cardiac or cerebral vascular events (Table 4) or minocycline use to delay the progression of multiple sclerosis.

We believe that essential aspects to consider when planning future therapeutic interventions based on MMP inhibition are the stages of the diseases in which the medications are used and the duration of exposure given side effects. Early use of MMP inhibition may have a more significant impact on disease progression as opposed to late stages, which tend to have a more relentless disease progression.

Tetracyclines are potent MMP inhibitors with good bioavailability in the central nervous system, and despite several therapy failures in neurological diseases, we consider that further studies are needed to evaluate whether these medications have a therapeutic role in neurological diseases.

Table 4 Ongoing studies related to MMP inhibition as a therapeutic strategy

| Study name ClinicalTrials.gov identifier | Estimated completion date | Estimated patient enrollment No | Population | Treatment | Control | Primary aim |
|---|---------------------------|---------------------------------|---|--|--|--|
| Neuroprotection in acute ischemic stroke (H2M) NCT03320018 | 2020 | 100 | Acute ischemic stroke within 24 h of last known well | Hydrogen i.v. tid for 3 days plus minocycline 100 mg once a day i.v. or PO for 5 days | Placebo hydrogen plus placebo minocycline | mRS at 45 and 90 days |
| PeRiodontale Treatment to Eliminate Minority InEquality and Rural Disparities in Stroke (PREMIERS) NCT02541032 | 2020 | 400 | Non-disabling stroke (mRS ≤ 3) or TIA in the past 90 days and periodontal disease | Intensive dental treatment plus minocycline | Intensive dental treatment | AIS, TIA, MI, and cardiovascular death at 1 year |
| Minocycline in MS: confirmation of benefit (MS) NCT04291456 | 2025 | 148 | Patients (18 – 60 years old) clinically isolated syndrome and at least 2 lesions on T2-weighted MRI | Minocycline 100 mg po bid for up 24 months | No control | Proportion of patients diagnosed with MS according to the 2005 McDonald criteria |
| Predictive value of infarction on hemorrhagic transformation in ischemic stroke/TIA with non-valve atrial fibrillation NCT03772457 | 2021 | 400 | Newly diagnosed ischemic stroke/TIA patients with NVAF and receive rivaroxaban | Rivaroxaban | NA | SWI detection of newly developed HT after 14 days of rivaroxaban treatment Predictive value of multi-mode MRI infarct volume and MMP-9 |
| Intensity-high NCT03355027 | 2020 | 60 | Patients with stable cardiovascular disease | Alirocumab 150 mg/ml + one of the following: atorvastatin 40/80 mg or simvastatin 80 mg or rosuvastatin 20/40 mg | Ezetimib 10 mg + one of the following: atorvastatin 40/80 mg or simvastatin 80 mg or rosuvastatin 20/40 mg | Primary outcome: Vascular inflammation (diverse parameters) Secondary outcome: Systemic inflammation, as measured by MMP-9 among others |
| The clinical trial of Chinese herbal medicine (SaiLuoTong) capsule NCT03789760 | 2023 | 500 | Patients with VaD | SaiLuoTong capsule: 375 subjects: 2 pills (120 mg) twice a day | 125 subjects with placebo | Vascular Dementia Assessment Scale-cognitive Subscale (VADAS-cog) at week 52 Alzheimer's Disease Cooperative Study-clinical Global Impression of Change (ADCS-CGIC) at week 52 Blood levels MMP-9 among other biomarkers |
| Evaluation of Xueshuantong in patients with acute ischemic stroke (EXPECT) NCT04415164 | 2023 | 480 | Patients with acute ischemic stroke | Xueshuantong lyophilized powder (500 mg) intravenous once a day for 10 days | Placebo | Change in NIHSS score on day 10 Change in MMP-9 level on day 10 Among other parameter |

Abbreviations: *mRS* modified Rankin Scale, *TIA* transient ischemic attack, *MI* myocardial infarction, *MS* multiple sclerosis, *NVAF* nonvalvular atrial fibrillation, *VaD* vascular dementia, *NIHSS* National Institutes of Health Stroke Scale, *SWI* susceptibility weighted imaging

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Declarations

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