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EXCEL Medical Bulletin

EXCEL Division of Blue Cross Laboratories

Azibest (Azithromycin) in Viral Infections

Azithromycin (AZM) is a synthetic macrolide antibiotic effective against a broad range of bacterial and mycobacterial infections. It also has an intriguing range of anti-viral and anti-inflammatory properties, and is now being investigated as a potential candidate for treatment of various viral infections.

A range of human in vitro and in vivo studies provide evidence of anti-viral activity of macrolides across a broad range of viral species and families like rhinovirus, zika virus, influenza A, enterovirus as well as corona viruses.

Azithromycin exhibits a variety of effects against these viruses and works differently on each of them.

- Rhino virus: Azithromycin reduces rhino virus replication and release in the primary human bronchial epithelial cells. The effect on viruses may relate to upregulation of intracellular adhesion molecule-1 (ICAM-1), a major receptor for rhinovirus.
- Influenza A: Azithromycin was shown to decrease the total leukocyte accumulation in lung tissue and broncheo-alveolar lavage, with the largest reduction being in neutrophils, and associated with decreased inflammatory mediators. Azithromycin also reduced the expression of viral proteins in H1N1 infections.
- Zika virus: Azithromycin reduced viral proliferation and virus-induced cytopathic effects in glial cell lines and human astrocytes and also suppressed Zika infection by targeting a late stage in the viral life cycle.
- Enterovirus: Azithromycin was shown to work through a common mechanism, after viral entry, impairing viral RNA synthesis either directly or indirectly.
- Coronaviruses: Azithromycin use was associated with an eightfold reduction in viral load of Alpha coronavirus and a 14-fold reduction in Beta coronavirus viral load. In case of the SARS CoV-2 virus, the treatment options were those that inhibited the replication of the virus which included ATPase proton pump inhibitors, protease inhibitors, viral protease inhibitors, drugs targeting the angiotensin pathway and azithromycin in which it was observed that azithromycin had an EC50 of 2.12μM and EC90 8.65, and selectivity index of >19, which is very comparable to the control compound remdesivir), the only anti-viral with proven clinical efficacy against SARS-CoV-2 in clinical trials to date.

Apart from this, another integral part of the treatment was immunomodulation where azithromycin showed beneficial effects.

ANTI-INFLAMMATORY EFFECTS OF AZITHROMYCIN

Whilst viruses can cause tissue damage by direct cytopathic effects on the infected cells, morbidity and mortality in severe disease are typically attributable to the host inflammatory response.

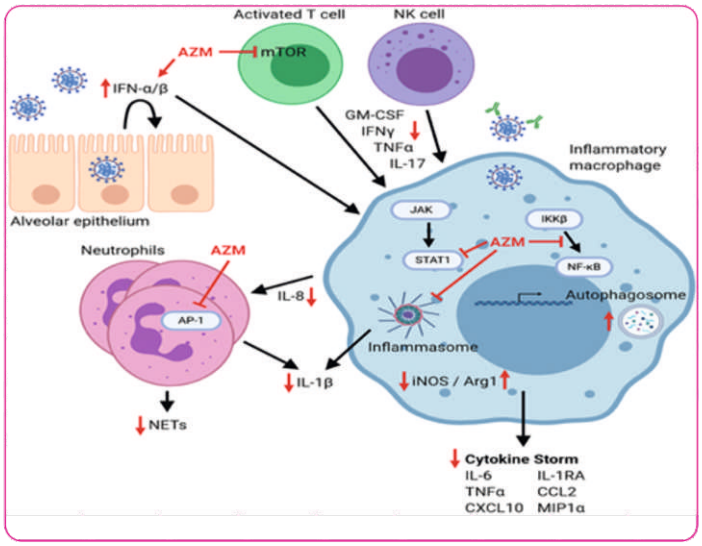
Azithromycin and other macrolides have a number of immunomodulatory properties which have proven clinical efficacy in a broad range of diseases including viral infections.

A striking feature of macrolides is that they can accumulate in host cells including epithelial cells and most particularly in phagocytes where they may concentrate 100- to 3000-fold in the lysosomes of phagocytes, being subsequently retained intracellularly and released when these cells die, keeping its concentrations high after one-three 500mg oral doses.

Azithromycin stimulates neutrophil degranulation and phagocytosis-associated oxidative burst. These initial stimulatory effects are followed by modulation of transcription factors activator protein (AP)-1, nuclear factor kappa B (NFκB), inflammatory cytokine and mucin release, with overall anti-inflammatory effects.

Many inflammatory cytokine levels are reduced by azithromycin, including IL-6, IL-8, TNF and GM-CSF, as well as matrix metalloproteases MMP-1, 2, 9, 10 and 13.

Azithromycin also inhibit mammalian target of rapamycin (mTOR) activity, important in T cell activation and granulocyte differentiation, suppressing cell proliferation and CD4 + T cell cytokine secretion.



It also suppresses p65, a component of NFκB and attenuates NFκB activation in lung epithelial cells which reduces epithelial cell IL-8 production, stromal cell proliferation and macrophage expression of IL-12p40 and, indirectly, Il-1β.

In macrophages, azithromycin has several effects including attenuation of lipopolysaccharide-induced pro-inflammatory cytokines, increasing phagocytosis, enhancing the resistance of lysosomes to oxidant challenge and promoting M2 polarization of macrophages.

Azithromycin can also increase the phagocytosis of apoptotic epithelial cells and neutrophils by macrophages, which can ameliorate inflammation.

Overall, azithromycin has a number of inhibitory effects on the production of pro-inflammatory cytokines from innate and adaptive immune cells, and most markedly on the accumulation, adhesion and apoptosis of pulmonary neutrophils.

As a therapeutic class, macrolides, and in particular azithromycin, with its long therapeutic half-life, good safety profile and very strong evidence base in bacterial diseases have been undoubtedly shown to have broad-spectrum anti-viral properties in vitro.

Azithromycin consistently emerges as a candidate molecule in anti-viral drug screens against various virus and especially respiratory viruses, with tantalising hints of clinical efficacy in clinical studies to date. The additional anti-inflammatory properties displayed by azithromycin, may well prove to be clinically important in reducing immunopathology in many viral diseases, not least against the current pandemic.

Source: Oliver ME & Hinks TSC. Rev Med Virol. 2020 Sep 23 : e2163.; Vincent J.Venditto et.al, Front. Immunol., 12 February 2021

Xstan (Telmisartan) As Ppar-ϒ/α Dual Activator: In The Management Of Non-alcoholic Fatty Liver Disease

"Fatty liver" is commonly associated with alcohol, however, more often it can happen in people who do not consume alcohol. Non-alcoholic fatty liver disease (NAFLD) is a build-up of extra fat in the liver, which is not related to alcohol. More than 98% of patients with NAFLD are either diabetic or obese. The global obesity and insulin-resistance pandemics have created a huge surge in NAFLD cases, making it the most prevalent hepatic disease and the primary reason for liver transplantation in the coming years. There is a vacuum in the treatment options of NALFD and can be mitigated with repurposing of existing drugs.

The excess of free fatty acids (FFA) gets accumulated in the hepatocytes and induces oxidative stress, inflammatory cascades and fibrosis development through several mechanisms.

Peroxisome proliferator-activated receptors (PPAR) are ligand inducible transcription factor under the class of nuclear receptor which perform diverse physiological functions such as metabolism, cellular development, and differentiation. There are three PPAR isotypes: PPAR-α, ϒ, and β/δ and they play an essential role as regulators of glucose, lipid metabolism, and energy equilibrium. PPAR-ϒ acts as the critical player of lipid

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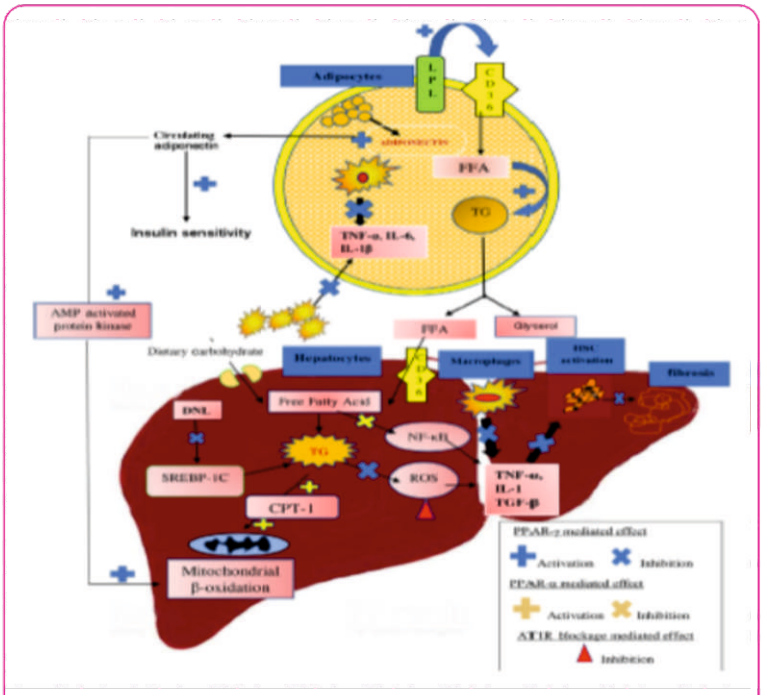
Thus there is evidence generated after the clinical applicability of telmisartan, a typical ARB as a PPAR-ϒ/α dual agonist in NAFLD management. Proposed pathways in protective effect of Telmisartan against NALFD



Proposed pathways in protective effect of Telmisartan against NALFD

Clinical studies like TRENDY, FANTASY etc. have demonstrated significant decrease in the FFA levels, improved insulin sensitivity and increase in the adiponectin levels improving the NALFD. The ability of telmisartan to activate PPAR-α was also contributed to this effect. Liver-specific PPAR-α gene activation by telmisartan was also reported. Telmisartan induced carnitine palmitoyltransferase 1A mRNA expression, a classical PPAR-α gene, increased fatty acid oxidation, and reduced hepatic and serum triglyceride.

Thus many preclinical and clinical studies have established the PPAR-ϒ/α dual activating property of telmisartan in addition to its angiotensin receptor blocking action. By these multitargeting properties, telmisartan may improve insulin sensitivity, control hypertension, increase the expression of genes related to beta-oxidation, fat deposition in adipocytes with concomitant downregulation genes linked to inflammation and oxidative stress and hence beneficial for the prevention and treatment for NAFLD.

PPAR-ϒ/α dual activation, favourable pharmacokinetics, excellent safety profile can replace telmisartan with synthetic glitazars and pave a new treatment option that could target all the disease components of NAFLD as well as comorbidities associated with NAFLD such as diabetes, hypertension, and dyslipidaemia.

Source: Aswathy R Devan et.al, Biotechnol Appl Biochem. 2021;1–8.

(MEGO XL) Vitamin B12 Deficiency and Ischemic Stroke Outcomes

Currently, ischemic stroke is the most prevalent form of stroke compared to hemorrhagic stroke and there is a high incidence in older adults, with nutrition being a modifiable risk factor.

B-vitamins are part of a metabolic network that integrates nutritional signals with biosynthesis, redox homeostasis, and epigenetics.

As we age, our metabolism and absorption of nutrients, including vitamins, also change. The most vulnerable to vitamin B12 deficiency is the elderly. However, a vitamin B12 deficiency can be caused by a reduced dietary intake, frequently in the case of a vegetarian diet, and or changes in absorption.

The high prevalence of a vitamin B12 deficiency in older adults is mostly due to malabsorption or increased atrophic gastritis, which leads to changes in gastric emptying and decreased secretion of intrinsic factor.

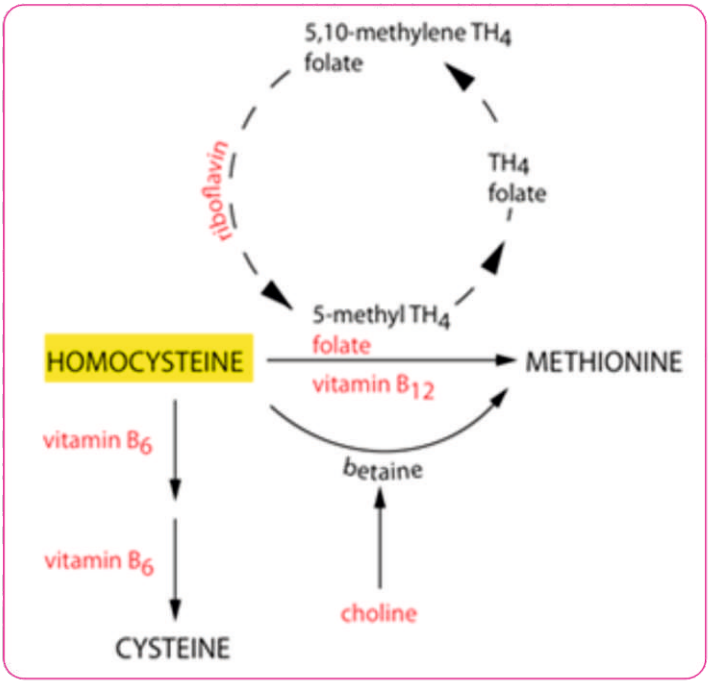
WHAT IS THE ASSOCIATION OF VITAMIN B12 AND THE BRAIN?

The brain has a minute to minute dependence on nutrient supply which can be impacted by dietary intake. In older adults, low levels of vitamin B12 have been linked to reduced cognitive function and Alzheimer's disease. Studies have shown that poor vitamin B12 status was significantly associated with greater severity of white-matter lesions in the brain, which may be a result of reduced myelin integrity. With aging, the transport mechanisms of getting vitamin B12 across the blood-brain barrier via receptor-mediated endocytic pathways become damaged. Furthermore, peripheral neuropathy is more common during vitamin B12 deficiency compared to other B-vitamin deficiencies.

Ischemic stroke is the result of blockage in blood flow within the brain that results in reduced oxygen and glucose, which leads to cell death and functional impairments. Nutrition, especially reduced levels of B vitamins, is a modifiable risk factor for stroke possibly through their role in metabolism of homocysteine.

Homocysteine is a sulphur amino acid whose metabolism stands at the intersection of two pathways:

- Re-methylation to methionine, which requires folate and vitamin B12
- Trans-sulfuration to cystathionine followed by cystiene, which requires pyridoxal-5'-phosphate.



ROLE OF B VITAMINS IN STROKE

Elevated levels of homocysteine increase the risk for vascular diseases, such as stroke. At the cellular level, increased levels of homocysteine lead to reduced levels of nitric oxide bioavailability, leading to changes in endothelial mediated dilation causing vascular damage due to the production of free radicals, as well as lipid peroxidation. The presence of atrial fibrillation, vitamin B12 deficiency, and resultant elevated levels of homocysteine which increases with age, are a risk factor for stroke.

B-vitamins metabolize homocysteine, therefore increasing levels of B-vitamins can be beneficial for patients with elevated levels of homocysteine in terms of reducing stroke risk.

VITAMIN B12 IN CLINICAL STROKE STUDIES

Various studies have been conducted to evaluate the role of vitamin B12 in strokes and outcomes from strokes.

In a longitudinal cohort study conducted on stroke cases, it was observed that increased intake of vitamin B12 was statistically significantly associated with a decreased risk of ischemic stroke and that the beneficial effects of intakes of folate, vitamin B6, and B12 were expected due to their inverse relationship with blood homocysteine.

A study has shown a 34% reduction of the risk of stroke, death or myocardial infarction in patients with a serum vitamin B12 level above the median (i.e., they could absorb the vitamin reasonably well) and received high-dose vitamins in comparison those with a serum vitamin B12 level below the median and received low-dose vitamins.

In another study it was observed that patients with a vitamin B12 deficiency during an ischemic stroke were reported to have worse outcomes post-stroke and low vitamin B12 levels were associated with more periventricular white matter lesions.

Vitamin B12 may thus play a key role in stroke prevention interventions that involve vitamin therapy for reducing high levels of homocysteine, which are linked to an increased risk of thrombosis and stroke. Another mechanism could be the role of vitamin B12 on neurological function, specifically to that of myelination.

However, the prevalence of metabolic vitamin B12 deficiency (not necessarily reflected in serum B12 levels) increases steeply with age, as do plasma total homocysteine levels.

Adequate levels of vitamin B12 are thus needed for successful aging especially with the clinical data and the results strongly suggesting that low levels of vitamin B12 are a risk factor for ischemic stroke.

Source: Gyllian B Yahan et.al, Neural Regen Res. 2021 Mar; 16(3): 470–474.

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