Amlexanox

JP Saleeby, MD

Priority Health Academy

theBODY

FLCCC

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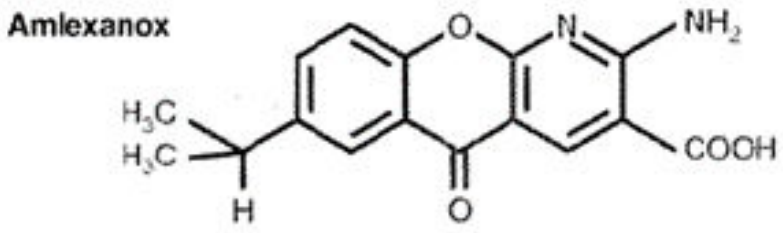


- Amlexanox (ALX) is FDA approved for canker sores/ recurrent aphthous ulcers. One trade name is Solfa® another is Aphthasol®. This drug fell out of favor in the USA in 2017 as other agents came to market.

- Class: tricyclic amine carboxylic acid. $C_{16}H_{14}N_2O_4$. It is a sister compound to sodium cromoglycate (SCG) Cromolyn®; Gastrocrom®; Nasalcrom®. It has excellent anti-inflammatory properties. anti-inflammatory, antiallergic, immunomodulator.

Uses

- Has been researched as an off-label drug for use in multiorgan damage due to COVID-19.
- Anti-inflammatory
- Can be uses as alternative to drugs with more ASE (e.g. Prednisone, MLK, etc.)
- 25mg or 50mg Tabs (by Takeda Pharma). (in one study with T2DM one cohort was administered 50mg TID [150mg/d])
- For aphthous ulcers a dose of 12mg/d is the normal (FDA approval for that use)

- At doses of 10mg/kg/day there were no ASE reported in a six-month toxicology study (in dogs)
- And in the rat model doses of 300mg/kg/d showed no carcinogenic or altered reproductive effects.

Approval and MOA

- Amlexanox is approved for use in asthma, conjunctivitis and rhinitis in Japan.

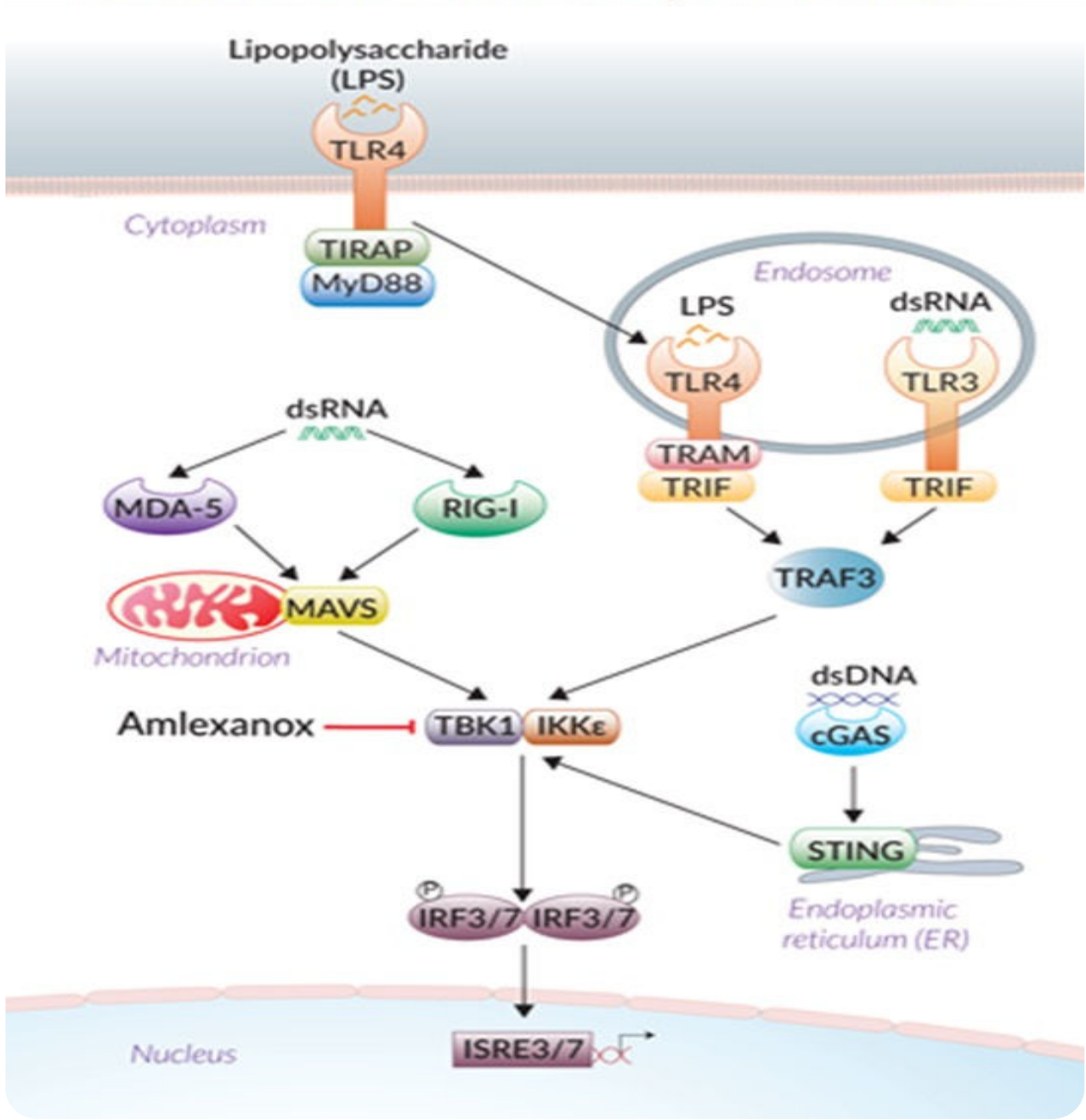
- It increases AMPK – cellular energy sensor that is activated by a fall in energy status with an increase in AMP to ATP. Restores energy homeostasis in the Krebs's cycle.
- It reduces mTOR – inflammatory pathway.
- It reduces NFk-B – inflammatory biomarker.
- Inhibitor of TBK1- IkB kinase TANK-1 and IKKε – IkappaB kinase-epsilon both components of interferon regulatory factor (IRF) signaling pathway. Elevations of TBK1 and IKKε are associated with several inflammatory diseases. Inhibition of this pathway reduces IL-33.
- Increases Autophagy

Approval and MOA

- Reduces Insulin Resistance (IR)
- Modulation of macrophages
- Th1:Th2 balance
- Reduces T-cell activation in neuroinflammation
- Reduces release of histamine and leukotriene mediators in mast cells, neutrophils and monocytes. Useful in MCAS and CIRS.
- In the mice model inhibits obesity related metabolic dysfunction
- Improvement in IRS and SBG in T2DM; Improvement in Fatty Liver Disease

- Rx at cPharm in the USA

TBK1/IKKε inhibition by Amlexanox



Can be used in place of

- H1 blockers (Antihistamine/ Zyrtec®, Claritin® and Benadryl®)
- H2 blockers (famotidine / Pepcid®)
- Leukotriene inhibitors (MLK / Singulair®)
- HD-Corticosteroids (Prednisone)

- Single agent can reduce dependence on other agents with more side-effects and ADS/cost

- Start with 40mg QD and can use up to QID. Pharma makes 25 & 50mg tablets available in Japan.

References:

Estrada E. Protein-driven mechanism of multiorgan damage in COVID-19. Med Drug Discov. 2020 Oct 20:100069. doi: 10.1016/j.medidd.2020.100069. Epub ahead of print. PMID: 33103107; PMCID: PMC7572300.

Reilly SM, Chiang SH, Decker SJ, Chang L, Uhm M, Larsen MJ, et al. An inhibitor of the protein kinases TBK1 and IKK-ε improves obesity-related metabolic dysfunctions in mice. *Nat Med*. 2013. March;19(3):313–21. 10.1038/nm.3082

Khandwala A, Van Inwegen RG, Alfano MC. 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: I. Clinical demonstration of acceleration of healing and resolution of pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1997. February;83(2):222–30. 10.1016/s1079-2104(97)90009-3 10.1016/S1079-2104(97)90009-3

He Q, Xia X, Yao K, Zeng J, Wang W, Wu Q, et al. Amlexanox reversed non-alcoholic fatty liver disease through IKKε inhibition of hepatic stellate cell. *Life Sci*. 2019. December;239:117010. 10.1016/j.lfs.2019.117010

Dosanjh A, Won CY. Amlexanox: A Novel Therapeutic for Atopic, Metabolic, and Inflammatory Disease. Yale J Biol Med. 2020 Dec 29;93(5):759-763. PMID: 33380937; PMCID: PMC7757066.

Imokawa S, Satou A, Taniguchi M, Toyoshima M, Nakazawa K, Hayakawa H, et al. [Amlexanox has an acute bronchodilator effect in patients with aspirin-induced asthma (AIA)]. *Nihon Kyobu Shikkan Gakkai Zasshi*. 1993. August;31(8):976–82

Yu J. *et al.***, 2015.** Regulation of T-cell activation and migration by the kinase TBK1 during neuroinflammation. Nat Commun. 6:6074.

Gonzalez-Hilarion S, Beghyn T, Jia J, Debreuck N, Berte G, Mamchaoui K, et al. Rescue of nonsense mutations by amlexanox in human cells. *Orphanet J Rare Dis*. 2012. August;7(1):58. 10.1186/1750-1172-7-58

Niederberger E. *et al.***, 2013.** The non-canonical IkB kinases IKKe and TBK1 as potential targets for the development of novel therapeutic drugs. Curr Mol Med. 13(7):1089-97.

Chiang SH. et al., 2009. The protein kinase IKKepsilon regulates energy balance in obese mice. Cell. 138(5):961-75.

Beyett TS, Gan X, Reilly SM, Chang L, Gomez AV, Saltiel AR, et al. Carboxylic Acid Derivatives of Amlexanox Display Enhanced Potency toward TBK1 and IKKε and Reveal Mechanisms for Selective Inhibition. *Mol Pharmacol*. 2018. October;94(4):1210–9. 10.1124/mol.118.112185

Makino H, Saijo T, Ashida Y, Kuriki H, Maki Y. Mechanism of action of an antiallergic agent, amlexanox (AA-673), in inhibiting histamine release from mast cells. Acceleration of cAMP generation and inhibition of phosphodiesterase. *Int Arch Allergy Appl Immunol*. 1987;82(1):66–71. 10.1159/000234292

Ozasa K, Temizoz B, Kusakabe T, Kobari S, Momota M, Coban C, et al. Cyclic GMP-AMP Triggers Asthma in an IL-33-Dependent Manner That Is Blocked by Amlexanox, a TBK1 Inhibitor. *Front Immunol*. 2019. September;10:2212. 10.3389/fimmu.2019.02212

Quan MY, Song XJ, Liu HJ, Deng XH, Hou HQ, Chen LP, et al. Amlexanox attenuates experimental autoimmune encephalomyelitis by inhibiting dendritic cell maturation and reprogramming effector and regulatory T cell responses. *J Neuroinflammation*. 2019. March;16(1):52. 10.1186/s12974-019-1438-z

Oral EA, Reilly SM, Gomez AV, Meral R, Butz L, Ajluni N, et al. Inhibition of IKKε and TBK1 Improves Glucose Control in a Subset of Patients with Type 2 Diabetes. *Cell Metab*. 2017. July;26(1):157–170.e7. 10.1016/j.cmet.2017.06.006

Phua EJ, Lopez X, Ramus J, Goldfine AB. Cromolyn sodium for insulin-induced lipoatrophy: old drug, new use. Diabetes Care. 2013 Dec;36(12):e204-5. doi: 10.2337/dc13-1123. PMID: 24265375; PMCID: PMC3836099.

Amlexanox Clinical Applications (Part I & II) by Dr. S. Halasa presentation June 2023

www.michiganmedicine.org/health-lab/repurposed-asthma-drug-shows-blood-sugar-improvement-among-some-diabetics

www.invivogen.com/amlexanox

www.raybiotech.com/amlexanox-332-10600#