Upadacitinib (ABT-494); selective JAK1 inhibitor

Eastern Pain Association

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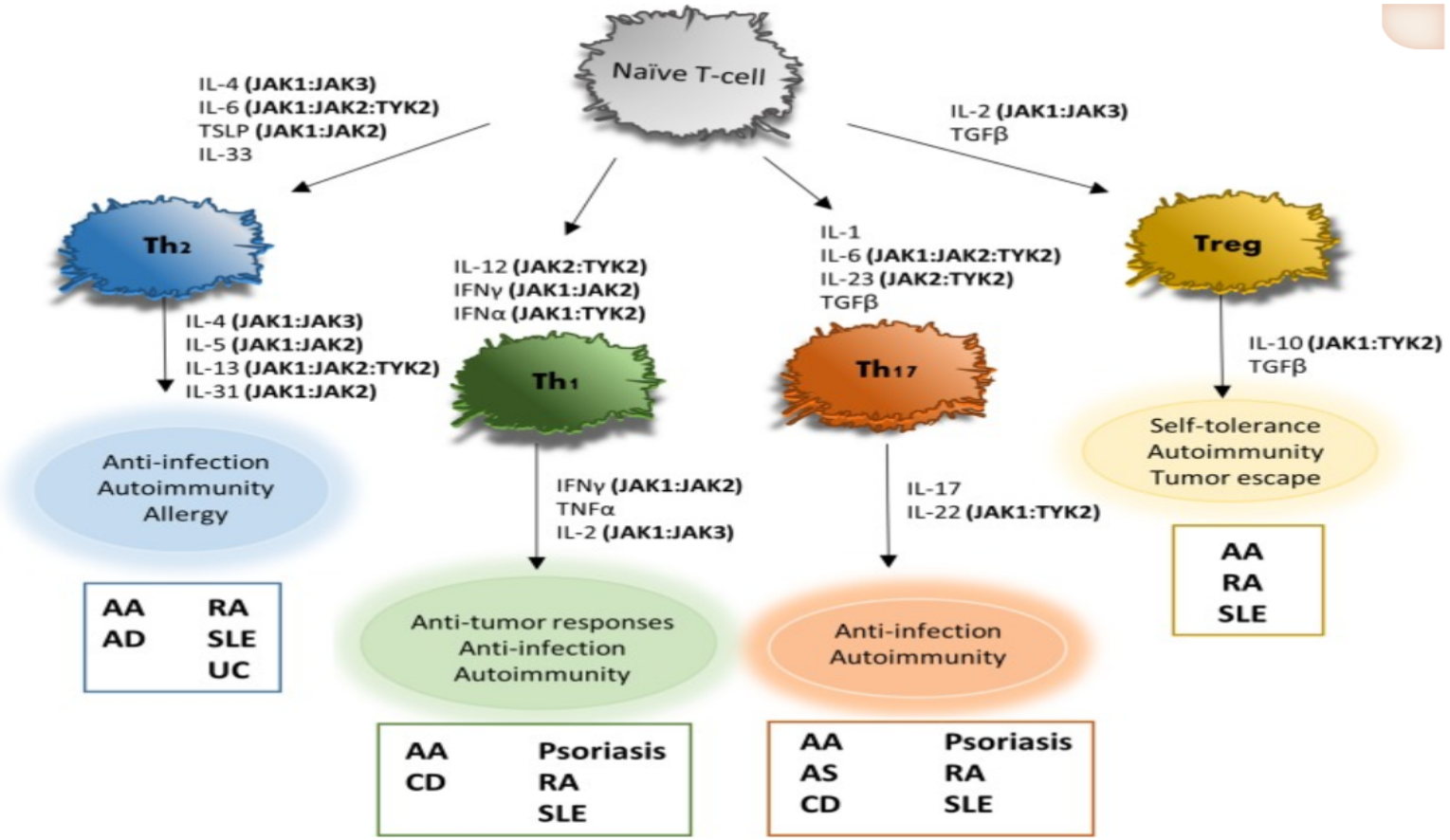
Background:
Janus Kinases (JAKs)

- Cytokines essential to cellular proliferation, survival, inflammation and immunity.
- Cytokine signaling Type 1 and 2 and downstreaming linked to inflammatory , autoimmune diseases and cancers
- This pathway is thought be essential in the development of variety of malignancies through production of cytokines (autocrine and paracrine) production, deregulation or mutations along the pathways.
- STAT3 through phosphorylation at Y705- elevated in cancers(head and neck, esophageal, non-small cell lung, breast, liver, pancreatic, colorectal, bladder and prostate). STAT3 present in approximately 70% of tumors
- JAK/ STAT (Signal transducer and activator of transcription) – important in cytokine and growth factor signaling.
- JAK-2 – role in hematoporesis



Selective JAKinibs: Prospects in Inflammatory and Autoimmune Diseases Virtenan, et al
doi: 10.1007/s40259-019-00333-w
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6373396/

Background

- Autoimmune diseases- particularly rheumatoid arthritis (RA) has been treated with biologics that target cytokines (TNF, IL-6, GM-CSF,CTLA4-Ig and CD20).
- DMARDS- methotrexate
- Inhibits lymphocyte proliferation, proinflammatory cytokines by enzyme suppression and JAK/STAT signaling
- Large molecules- administered by SC/IV

- Family of Janus Kinases (JAK-1, JAK-2, JAK-3 and Tryosine Kinase (TRYK-2)
- Non Biologics -
- tofacitinib (Pfizer) JAK-1/JAK-3 inhibitor- RA, psoriatic arthritis and ulcerative colitis
- ruxolitinib (Incyte/Novartis) JAK1/JAK2 inhibitor- myeloproliferative neoplasms
- baricitinib (Lily) JAK-1, JAK-2, TRYK-2 relative to JAK-3

JAK Adverse effects

- tofacitinib
- headache, infection, decrease CD+4 T cell count, elevated cholesterol levels (LDL/HDL), increase in serum creatinine levels (reversible), herpes zoster, gastric perforation, venous thromboembolism.
- ruxolitinib

- baricitinib
- nausea, URI, elevated cholesterol, herpes -zoster, simplex, UTIs, thrombocytosis and hepatobiliary disorders.

JAK-1

- JAK-1 signals with JAK-2 via IFN-γ receptor
- Pairs with JAK-2 and TYK-2 to signal through glycoprotein receptors (cytokines IL-6, IL-11 and IL-27)
- JAK-1 inhibitors spares JAK-2 dependent erythropoietin and thrombopoietin pathways. (Avoiding anemia, thrombocytopenia and neutropenia)

Upadacitinib

- JAK-1 selective inhibitor
- Invitro selectivity- 74 fold JAK-2
- 58 fold JAK-3

- STAT-3 phosphorylation driven by IL-6 and IFN-γ was blocked ;
- STAT-5 phosphorylation was modulated at 60 fold higher concentration- resulting in potency against inflammatory cytokine diseases and minimizes the EPO signaling.
- Effects on hemoglobin and Natural Killer (NK) cells – dose dependant
- Starting dose 3mg BID- significant clinical improvement 6 mg BID
- >6mg BID resulted in greater decrease of Hgb and NK

Upadacitinib

- RA patients
- Did not respond to methotrexate or TNF inhibitors
- Had response after 2 weeks- improved clinical symptoms
- Dose dependent effects- elevated LDL/HDL
- Reduced Hgb levels

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