Mitigation of Inflammation Induced By Monosodium Urate Crystals in Mice By Treatment with SVP-Rapamycin

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Abstract

Background/Purpose: Initiation of urate-lowering therapies is typically associated with an increase in gout flares due to mobilization of pro-inflammatory urate crystals. SEL-212 is a novel combination product candidate consisting of pegadricase (formerly known as pegsiticase), a pegylated uricase, co-administered with synthetic vaccine particles encapsulating rapamycin (SVP-Rapamycin) being developed for the treatment of chronic severe gout. Data from the ongoing open-label Phase 2 multidose study of SEL-212 indicate that SVP-Rapamycin mitigates the formation of anti-drug antibodies (ADAs) against pegadricase, enabling monthly dosing and sustained control of serum uric acid (SUA) levels in most patients. Despite rapid and sustained reduction of SUA, patients treated with SEL-212 experienced a low rate of flares. Here we evaluated in animal studies whether SVP-Rapamycin might have a beneficial effect on reducing inflammation induced by monosodium urate crystals (MSU) in addition to its effects on mitigating the formation of ADAs.

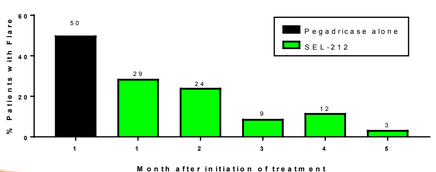
Methods: MSU-induced inflammation was investigated in an air pouch model in C57Bl/6 mice. An air pouch was generated on the dorsal aspect of a mouse by injecting sterile air on d0 and d3. Mice were treated intravenously with placebo or SVP-Rapamycin on d7. MSU crystals were injected in the air pouch on d8 and mice were sacrificed 5 hours after MSU injection. Air pouch exudate was analyzed for cellularity and interleukin-1β (IL-1β) levels as markers of inflammation.

Results: Injection of MSU crystals into the air pouch of a mouse has been previously shown to induce an acute inflammatory response characterized by expression of IL-1β and an influx of neutrophils. Intravenous administration of SVP-Rapamycin reduced the generation of IL-1β in the air pouch exudate and the number of Ly6G+CD11b+ neutrophils.

Conclusion: SVP-Rapamycin has been shown to mitigate the formation of ADAs to biologic therapies by inducing tolerogenic dendritic cells and antigen-specific regulatory T cells. Here we demonstrate that SVP-Rapamycin also attenuates inflammatory responses induced by MSU crystals and mediated by innate immune cells. These results may explain why gout patients treated with pegadricase in combination with SVP-Rapamycin experience a low rate of gout flares.

SEL-212

- SEL-212 is a combination drug candidate comprised of pegadricase (formerly known as pegsiticase) and SVP-Rapamycin
- SVP-Rapamycin is designed to induce the formation of regulatory T cells that mitigate the formation of anti-drug antibodies (ADA) (Kishimoto et al, 2016, Nature Nanotech)
- Ongoing Phase 2 clinical trial of SEL-212 has demonstrated low incidence of ADAs resulting in sustained reduction of serum uric acid (SUA) with monthly dosing (see Abstract 2254)
- Patients on SEL-212 therapy experienced a low level of gout flares (see Abstract 1294)



Background

Gout Flares

- Acute gout attacks are characterized by a rapid onset of pain in the affected joint followed by warmth, swelling and pain[1]
- 69% of gout patients describe the pain of an attack as "miserable", 23% of patients compare the pain of a gout attack to shattered glass piercing their skin, 28% to breaking a bone, 34% to a severe burn[2]
- Most people with gout will experience repeated bouts over the years

[1]www.uptodate.com/contents/treatment-of-gout-flares
[2]www.webmd.com/arthritis/news/20100611/gout-survey-offers-peek-at-the-pain

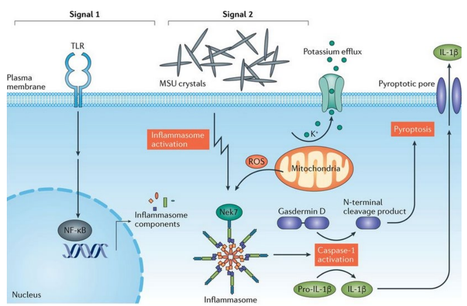
Effect of Urate Lowering Therapies on Gout Flares

- Dispersion of MSU crystals during the initial phase of deposit dissolution exposes the patient to an increased rate of acute flares
- Increased gout flare can adversely affect patient compliance[3]
- Pegylated uricase therapy, which rapidly debulks tissue uric acid, has been reported to induce gout flares in 75% of patients in the first months after initiation of therapy[4]

[3]Becker MA et al., Nucleic Acids 2008 27:585-91
[4]Sundy et al, JAMA, 306 7:711-720

MSU crystals induce activation of the inflammasome

- Monosodium urate (MSU) crystals induce inflammation through activation of NLRP inflammasomes resulting in production of the pro-inflammatory cytokine IL-1β



Ko and Matinon, Nature Rev Rheumatol, 2017, 13:639-647

Potential effect of SVP-Rapamycin on inflammation

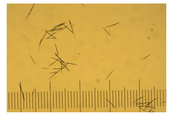
- Rapamycin has been reported to inhibit inflammasome activation[5]
- Here we evaluated the effect of SVP-Rapamycin on inflammation induced by MSU crystals in mice

[5]Ko et al., 2017, Oncotarget 8:40817-40831

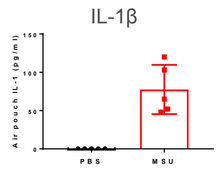
Results

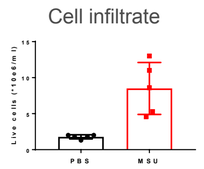
Air pouch model of MSU-induced inflammation

Monosodium urate crystals

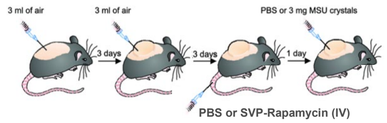


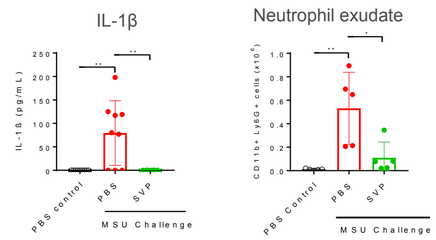
- C57BL/6 mice injected with sterile air subcutaneously on d0 and d3.
- MSU crystals injected into air pouch on d6
- Sacrifice mice after 6 hours to collect exudate





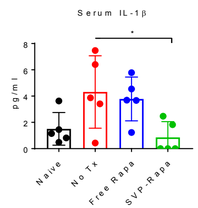
SVP-Rapamycin inhibits MSU-induced inflammation in air pouch





SVP-Rapamycin but not free rapamycin inhibits MSU-induced IL-1β

- C57BL/6 mice I.V. treated with SVP-Rapamycin or free rapamycin
- Injected I.P. with MSU crystals 16 hours after treatment
- Serum IL-1β assessed 6 hours after MSU challenge



Summary

- Initiation of urate lowering therapy can increase the incidence of gout flares which can adversely affect patient experience and compliance
- Here we show that SVP-Rapamycin treatment can mitigate IL-1β production and neutrophil infiltrates in a monosodium urate-induced model of inflammation in mice
- An ongoing Phase 2 clinical trial of SEL-212 has demonstrated low incidence of anti-drug antibodies resulting in sustained reduction of serum uric acid (SUA) with monthly dosing (see Abstract 2254)
- The incidence of gout flares after the initiation of SEL-212 therapy was lower than anticipated (See Abstract 1294)
- SEL-212 may have the additional benefit of reducing gout flares by inhibiting inflammation despite rapid and sustained lowering of SUA

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Disclosures

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