Mitigation of Anti-Drug Antibodies Against a Pegylated Uricase in Patients with Hyperuricemia Results in Enhanced Control of Serum Uric Acid

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Abstract

The development of anti-drug antibodies (ADAs) is a common cause for biotherapeutic treatment failure and adverse hypersensitivity reactions. We have previously demonstrated that synthetic vaccine particles encapsulating rapamycin (SVP-Rapamycin), but not free rapamycin, are capable of inducing durable immunological tolerance to biologic drugs, resulting in improved efficacy in disease-relevant animal models (Kishimoto et al., Nature Nanotech 2016). Here, we report on our translation of these findings to humans by demonstrating that the addition of SVP-Rapamycin to pegsiticase, a pegylated uricase enzyme, mitigated the formation of ADAs, enabling sustained control of serum uric acid (sUA) levels for at least 30 days after a single dose in patients with hyperuricemia (sUA >6 mg/dl) in a Phase 1 open-label multicenter clinical trial conducted in the USA. Most patients dosed with pegsiticase alone showed an immediate drop in sUA, which returned to baseline hyperuricemic levels by 14-21 days, correlating with the induction of anti-uricase antibody titers >1:1000. Patients treated with SVP-Rapamycin alone showed no meaningful change in sUA. In contrast, those treated with SEL-212, the combination of SVP-Rapamycin and pegisiticase, showed a dose-dependent inhibition of anti-uricase ADAs with resulting maintenance of uricase enzyme activity and a corresponding decrease in sUA levels through at least day 30 after a single injection. There was a strong correlation between maintenance of low uric acid levels at day 30 and low or no ADA titers. These results supported monthly dosing in an ongoing Phase 2 multi-dose study in symptomatic gout patients and the potential use of SVP-Rapamycin to mitigate ADAs for other immunogenic biologics.

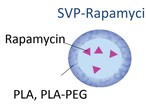
Background

Pegsiticase

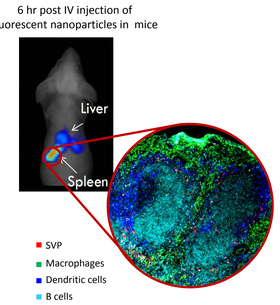
Pegsiticase

- Uricases have been shown to be very effective in significantly reducing serum uric acid levels in patients with chronic refractory gout
- The currently marketed uricase, Krystexxa (pegloticase), is highly immunogenic, compromising its safety and efficacy (Sundy et al, JAMA, 2011)
  - 92% of patients develop anti-drug antibodies
  - 58% of patients lose efficacy
  - Risk of infusion reactions and anaphylaxis
- Pegsiticase is a different pegylated uricase enzyme that is being developed in combination with SVP-Rapamycin to mitigate its immunogenicity

SVP-Rapamycin

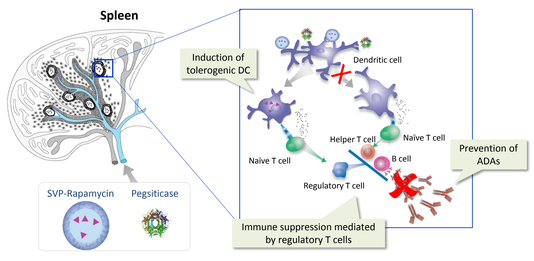


- SVP-Rapamycin is a biodegradable nanoparticle that encapsulates rapamycin, an mTOR inhibitor
- Intravenous injection of SVP-Rapamycin results in selective accumulation in the spleen and liver, where it is endocytosed by dendritic cells (DC) and macrophages
- SVP-Rapamycin is designed to be co-administered with biologic drugs to prevent the formation of ADAs through the induction of immune tolerance and thus enable sustained therapeutic activity of the biologic



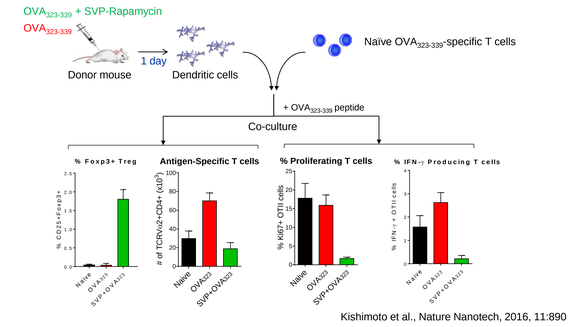
SEL-212

- SEL-212 is a combination drug comprised of pegsiticase and SVP-Rapamycin
- The co-administration of SVP-Rapamycin and pegsiticase is designed to induce the formation of regulatory T cells that prevent the formation of ADAs against pegsiticase and enable sustained reduction of serum uric acid (sUA) levels



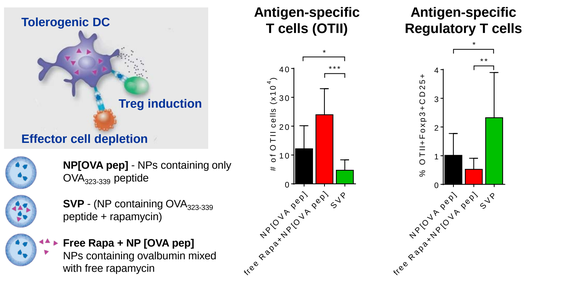
Preclinical Efficacy

Tolerogenic dendritic cells induced in vivo by SVP-Rapamycin



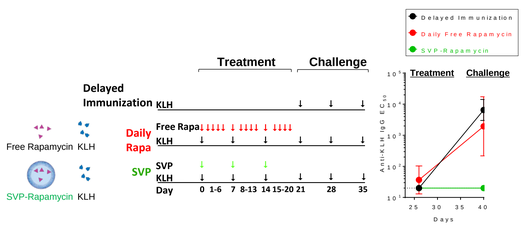
Kishimoto et al., Nature Nanotech, 2016, 11:890

Antigen-specific regulatory T cells induced in vivo by SVP-Rapamycin



Maldonado et al., PNAS, 2015, 112: E156

Encapsulation of rapamycin is required for tolerance induction



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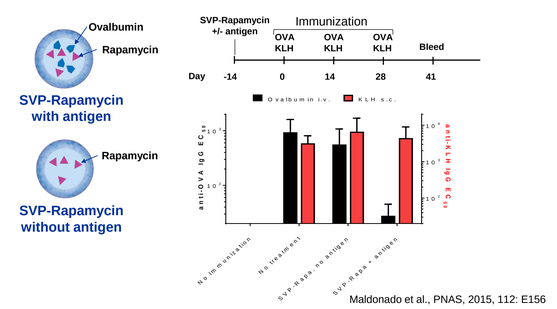
Tolerance induction is antigen-specific



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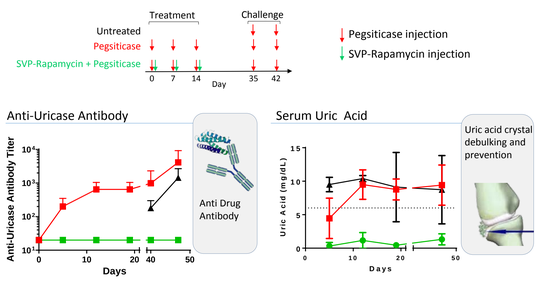
SEL-212 prevents ADAs and lowers sUA levels in uricase-deficient mice



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Phase 1a Clinical Trial

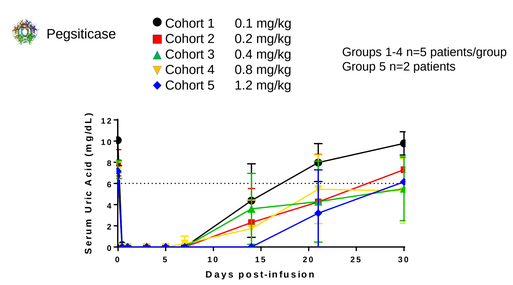
Trial	Design	Objective
Phase 1a	• n = 22 • Single dose of pegsiticase • Patients with hyperuricemia	✓Evaluate safety and tolerability ✓Define effective dose of pegsiticase ✓Demonstrate formation of ADAs clinicaltrials.gov NCT02464605

Clinical trial design

Study description

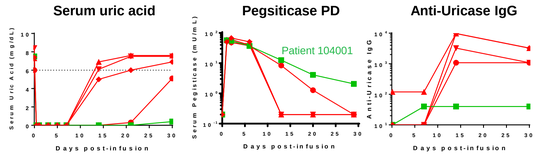
- Evaluated the safety, pharmacokinetics, pharmacodynamics and immunogenicity of a single IV infusion of pegsiticase in patients with elevated serum uric acid levels (sUA >6 mg/dL)
- Cohorts of patients were administered a single IV infusion of 0.1, 0.2, 0.4, 0.8, or 1.2 mg/kg pegsiticase
- Monitored for safety, uric acid levels and ADAs to pegsiticase for 30 days
- Male or female subjects ages 21 to 75

Reduction and rebound of sUA levels after a single dose of pegsiticase



Patient with low ADA titer maintains low sUA levels for 30 days

Cohort 3 (0.4 mg/kg)– Individual patient data (n=5)



Subject number	Baseline		Day 7		Day 14		Day 30	
	Uric acid (mg/dL)	ADA (Titer)	Uric acid (mg/dL)	ADA (Titer)	Uric acid (mg/dL)	ADA (Titer)	Uric acid (mg/dL)	ADA (Titer)
103003	7.4	Neg	<0.1	Neg	5	9720	6.9	3240
104001	7.5	Neg	<0.1	40	<0.1	40	0.4	40
104002	7.3	120	<0.1	120	6.9	9720	7.6	3240
104004	7.6	Neg	<0.1	Neg	6.1	3240	7.5	1080
104008	4.9	Neg	<0.1	Neg	<0.1	1080	5.1	1080

Patient 104001 data indicate that in the absence of high titer ADAs, control of serum uric acid levels can be maintained for 30 days after a single injection of 0.4 mg/kg pegsiticase

Safety and tolerability of pegsiticase

Pegsiticase

- Pegsiticase was generally well tolerated at all tested doses
- No SAEs observed

Phase 1b Clinical Trial

Trial	Design	Objective
Phase 1b	• n = 63 • Single dose of SEL-212 • Patients with hyperuricemia	✓Evaluate safety and tolerability ✓Demonstrate mitigation of ADA formation ✓Demonstrate prolonged control of uric acid levels clinicaltrials.gov NCT02648269

Clinical trial design

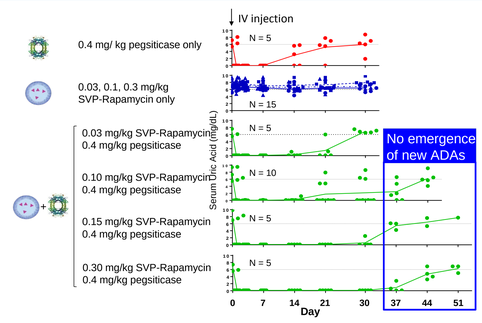
Study description

- Evaluated the safety, pharmacokinetics, pharmacodynamics and immunogenicity of repeated monthly IV infusions of SEL-212 in patients with elevated serum uric acid levels (sUA >6 mg/dL)

Cohorts

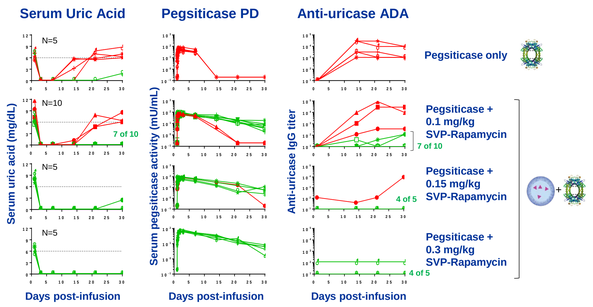
- Pegsiticase only cohort: 0.4 mg/kg pegsiticase
- SVP-Rapamycin alone cohorts: 0.03, 0.1, 0.3, or 0.5 mg/kg SVP-Rapamycin
- SEL-212 cohorts: 0.03, 0.1, 0.15, or 0.3 mg/kg SVP-Rapamycin in combination with a fixed dose of 0.4 mg/kg pegsiticase

Dose-dependent reduction of sUA with SEL-212 in hyperuricemic patients



Single dose of SEL-212 can maintain low sUA levels for at least 30 days after a single dose

Correlation of ADA titers with sUA and pegsiticase PD



Safety and tolerability of SEL-212

SVP-Rapamycin alone

- 17x dose range tested to determine maximum tolerated dose (MTD)
- At 0.5 mg/kg, two SAEs (stomatitis), a known side effect of rapamycin. Resolved

SEL-212 (combination of SVP-Rapamycin and pegsiticase)

- Generally well tolerated at clinically active dose levels (0.1, 0.15 or 0.3 mg/kg SVP-Rapamycin + 0.4 mg/kg pegsiticase). No dose-dependent trends
- At 0.1 mg/kg SVP-Rapamycin + pegsiticase there was one SAE (grade 2 rash). Resolved
- No SAEs at 0.15 or 0.3 mg/kg SVP-Rapamycin + pegsiticase

Conclusions

- Pre-clinical studies show that SVP-Rapamycin induces antigen-specific immune tolerance through the induction of tolerogenic DCs and Tregs
- SVP-Rapamycin mitigates the formation of ADAs when co-administered with a biologic drug
- The Phase 1a clinical trial shows that pegsiticase, similar to other uricases, is highly immunogenic after a single dose
- The Phase 1b clinical trial of SEL-212 (pegsiticase + SVP-Rapamycin) shows dose-dependent inhibition of the formation of ADAs enabling maintenance of serum uricase enzyme activity and resulting in sustained control of serum uric acid levels for at least 30 days after a single dose, supporting a monthly dosing regimen in Phase 2
- SEL-212 was well tolerated at clinically active dose levels
- Initial data from the SEL-212 Phase 2 study will be presented as a late-breaking talk Thursday at 4:45 PM (Abstract T.68)

Acknowledgements: We thank all of the patients that participated in these clinical trials. We are very grateful to the clinical trial site investigators and the entire Selecta SEL-212 project team