PerioTrap

Poster: 20

Non-clinical development of a minocycline containing controlled releasing periodontal insert

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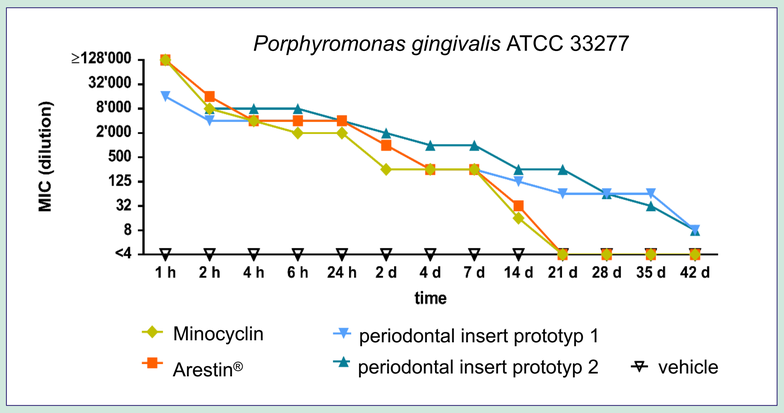
Introduction

Chronic periodontitis is triggered by the accumulation of oral bacteria, particularly of *P. gingivalis*, and the resulting microbial shift to a pathogenic microflora [1]. If untreated, the prolonged inflammation leads to soft and hard tissue destruction. Current periodontitis therapy often consists of scaling and root planning and adjunctive, application of topical antibiotics in form of gel (Ligosan®) or microspheres (Arestin®) [2, 3]. By far the most promising and effective treatment, available currently only on the U.S. market, is Arestin®, microspheres releasing minocycline hydrochloride, that can significantly improve the benefits for the patient. However, the application of Arestin® requires specialized skills and equipment which reduces the acceptance. This reflects the need of a new pharmaceutical product which exhibits in addition to an easy usage a prolonged antimicrobial effect and biodegradability. A novel periodontal insert, developed by PerioTrap Pharmaceuticals GmbH, combines all these features. This pharmaceutical composition contain minocycline in a defined complex with magnesium stearate in form of a flexible threat.

Antimicrobial effect of periodontal inserts



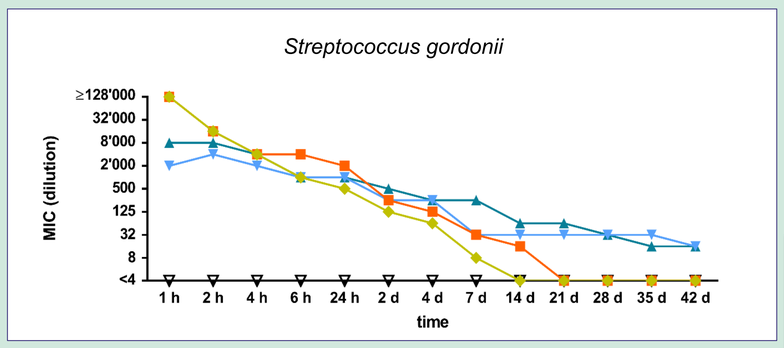
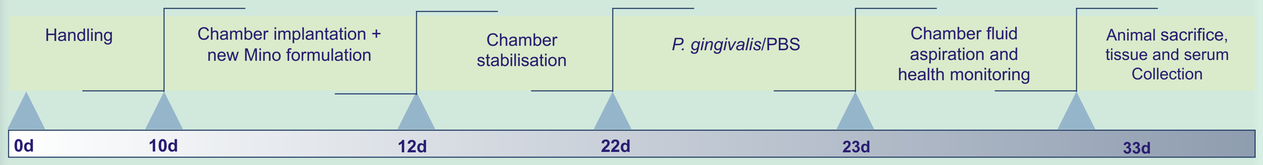


Fig. 1: Determination of antimicrobial effect of novel periodontal insert in comparison of Arestin® and minocycline as pure compound

The new pharmaceutical formulation was tested for it's release of the broad spectrum anti-biotic minocycline *in vitro and* compared with the pure compound as well as with Arestin®, Thereby the GCF-flow was modelled by regularly exchange of the release medium over 42 days. In addition, the effect of the formation of a six-species biofilm was tested, with comparable results for pure minocycline, Arestin® and the novel periodontal insert (data not shown).

Periodontal inserts reveal a prolonged antimicrobial effect compared to Arestin® [4]

Proof of concept I – mouse chamber model



For the first PoC in mice, the chamber model as described above was used. 6 groups of pathogen-free Balb/c mouse (5 different dosages + negative control) were formed. After 8 days post infection the animals were sacrificed, serum samples were collected and different inflammation markers (TNFα, IL6, IL10) as well as the systemic minocycline level was determined. The systemic burden with minocycline was neglectable even in the group with the highest dosage of 80 mg/kg (data not shown).

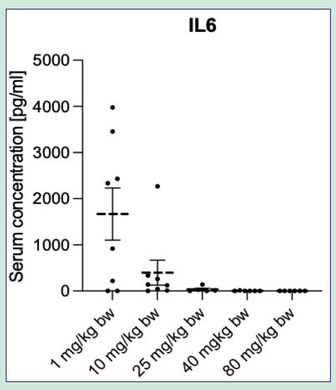


Fig. 2: Determination IL6, a pro-inflammatory cytokine, in mouse serum samples

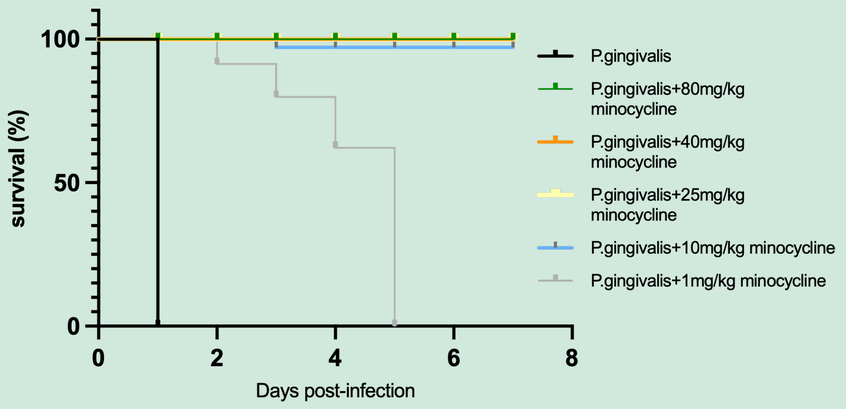
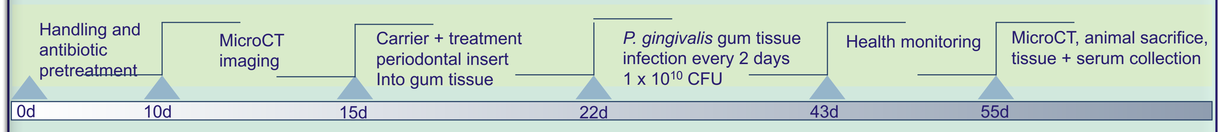


Fig. 3: Dose dependent effect on the survival curves after infection

Periodontal inserts provide dose depended protection of *P. gingivalis* mediated toxicity and immune response [5]

Proof of concept II - rat ligature model



The novel formulation was applied in a dosage of 20 mg/kg BW by 6 microinjections (35 ul per side - inner outer 30G) in 1st, 2nd and 3rd molar sites. The systemic burden of minocycline was measured and determined by HPLC/MS/MS and found to be neglectable (LLOQ < 5 ng/mL) with the used effective dosage.

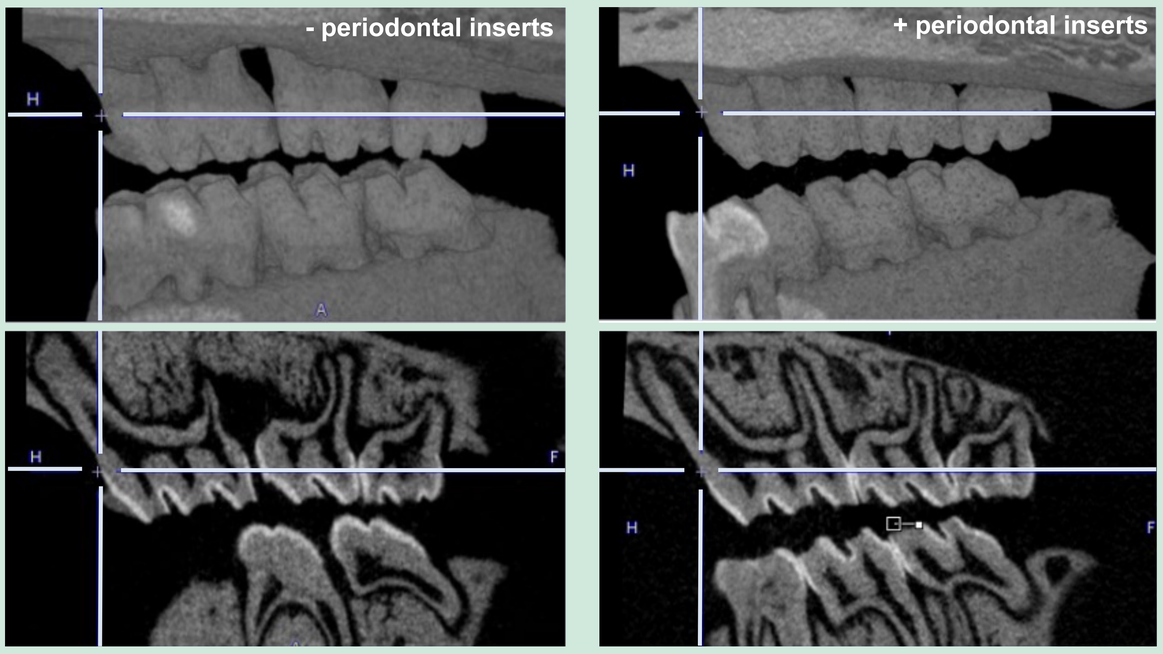
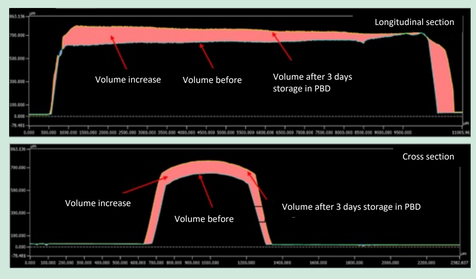


Fig. 4: 2-D representation of rat heads MicroCT scans. Each evaluation consist of 12 measurements.

Periodontal inserts reduce *P. gingivalis* mediated tissue and bone loss

Swelling and Degradation

The novel periodontal insert were placed into PBS-buffer without light exposure and under slightly shaking conditions to investigate the ability of a self-degradation over time. After several time points the threads were analysed under a scanning electron microscope (SEM). The swelling behaviour was measured by laser scanning microscope (LSM) in a comparable set-up over 11 days.



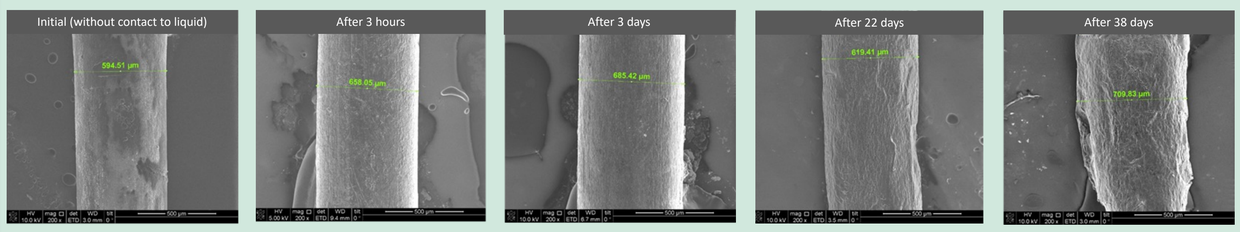
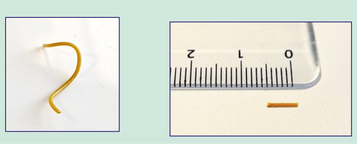


Fig. 5: LSM images (upper right) at day 0 and day 3 in different views. The difference in swelling is coloured in red. SEM images at 200 x magnification (lower row) of the periodontal inserts at different time points.

Periodontal inserts swell for the first days before slow self-degradation starts

Flexibility

The novel periodontal inserts are produced based on a bio-polymer with a diameter of 0.6 mm. 3 pieces are one dosage to be placed into the periodontal pockets. The dentist can easily handle it without any additional device. Because it is bio-degraded, it will not be removed from the pocket.



Periodontal inserts exhibit flexibility, an appropriate size and can be easily placed

Conclusion

PerioTrap developed a novel pharmaceutical composition containing well-known minocycline as active ingredient, which is stabilized for an effect duration in the pocket over weeks. This new composition revealed (1) a prolonged controlled release compared to Arestin®, (2) a good efficacy in different PoC- animal models, (3) the ability to self-degradation and (4) an easy application. Based on this, the insert will be clinical tested starting at the end of 2023 and will be further developed to provide a sustainable solution for a local adjuvant periodontitis treatment.

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[3] Goodson, J.M. *et al.* (2007) Minocycline HCl microspheres reduce red-complex bacteria in periodontal disease therapy. J Periodontol. 2007 Aug;78(8):1568-79
[4] Schmid, J.-L. *et al.* (2020) In Vitro Evaluation of Antimicrobial Activity of Minocycline Formulations for Topical Application in Periodontal Therapy. Pharmaceutics 2020 Apr 13;12(4):352
[5] manuscript in preparation

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