Use of MRI to quantify intra-vaginal gel distribution in human subjects: preliminary analysis of the candidate gel formulation for the Cyanovirin-N trial.

M. Rosen[1], A. Hummel[1], K. Timbers[1], D. Shera[1], S. Pretorius[1], F. Malinoski[2], K. Barnhart[1]

[1]University of Pennsylvania, Philadelphia, PA, United States, [2]Biosyn, Inc., Huntingdon Valley, PA, United States

Background: Topical intra-vaginal microbicides, including those directed against HIV have been proposed as a means of protecting against disease transmission. These microbicides are intended to cover the vaginal mucosa, acting as a physical and chemical barrier toward infection. However, for optimal clinical efficacy, distribution across the entire vaginal epithelium is desirable. MRI has previously been used as a means of tracking the distribution and spread of intra-vaginal gels (1-3). In this study, four potential gel formulations without active antimicrobial agent were studied in a phase II trial to determine which gel demonstrates optimal vaginal coverage for use in an upcoming clinical trial of Cyanovirin-N.

Methods: Six normal female volunteers (age 21-30) were enrolled in a randomized trial to study the effects of gel type, time of insertion, and simulated sexual intercourse on intra-vaginal distribution and spread of each gel. The study was approved by the local institutional review board. Each subject underwent two MRI examinations each following immediate or delayed (four hours) insertion of each of four vaginal gels doped with Magnevist© (Berlex, Wayne, NJ), for a total of eight exams. Three-dimensional T1 FLASH series were performed on a 1.5T magnet (Symphony©, Siemens, Erlangen, Germany). A single MR radiologist measured the longitudinal, transverse, and AP spread of gel at each of five pre-determined landmarks [**Figure 1**] for each T1 weighted data set. Mean absolute and relative vaginal mucosal coverage was computed for each gel. Differences in mean vaginal coverage between gels were evaluated through an ANOVA. Significance in each case was determined at a p=0.05 level.

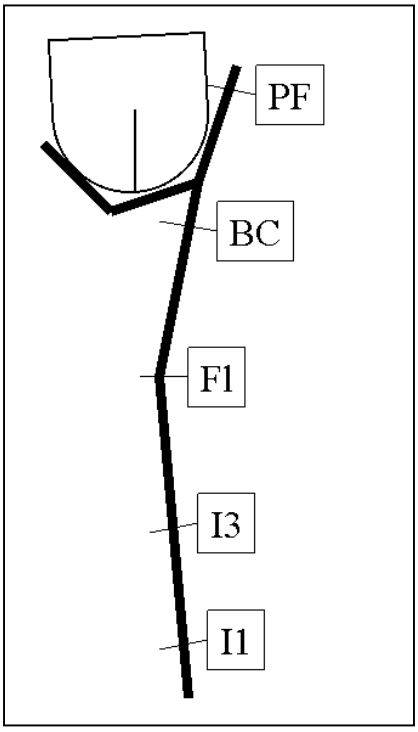

Figure 1 [above]: Schematic diagram of the vagina. Anatomic landmarks for study are indicated. PF) posterior fornix, BC) 1cm below cervix, Fl) vaginal flexure, I3) 3cm above introitus, and I1) 1cm above introitus.

Results: Simulated intercourse resulted in improved distribution for all four gels. Gel B improved the greatest amount (55%→70% coverage), while gel D improved the least (65%→69% coverage). There were no significant differences in vaginal coverage between gel types after simulated intercourse. Delay between insertion and imaging (four hours) improved vaginal coverage in gel B and gel D by 16% and 10%, respectively, but had negligible effects on gels A and C. Across all measurement time points, relative vaginal coverage for gels A through D was 70%, 62%, 63%, and 67%, respectively (p=NS). However, there was a significant difference between gel distributions immediately after insertion (p=0.028), and a significant difference in coverage below the cervix after simulated intercourse (p=0.014). **Figure 2** demonstrates distribution differences for two different gels immediately post insertion in one of the volunteers.

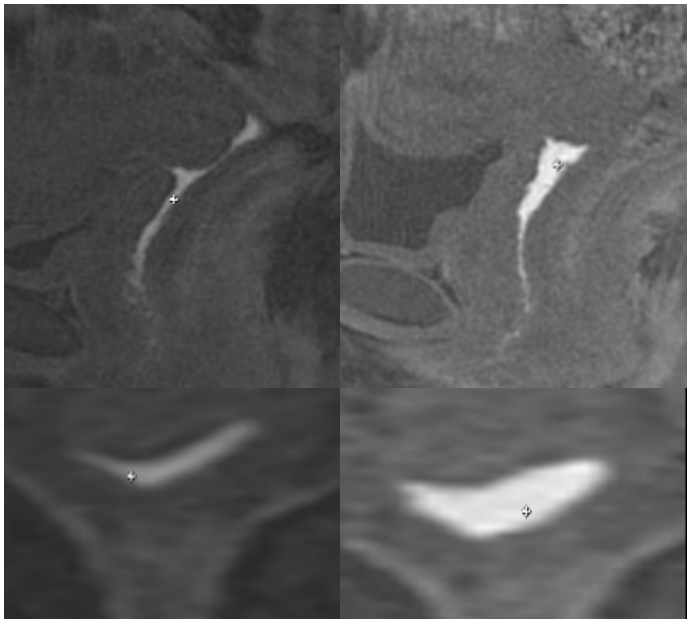

Figure 2: Comparison of gel distributions for two different gel formulations, immediately upon insertion. Top, sagittal slice from 3D FLASH sequence. Bottom, reformatted oblique transverse multi-planar reformatted (MPR) image at level 1 cm below cervix [point **BC** in Figure 1]. Note that transverse spread is similar between the two gels, but longitudinal coverage is improved for the gel on the left.

Conclusion: MRI is easily able to demonstrate and quantitate intra-vaginal distribution of gel in human clinical trials. Such trials enable physiologic evaluation of gel coverage of vaginal epithelium. These results are useful for evaluating different gel formulation and methods of application for clinical trials of intra-vaginal microbicides.

References:

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