White Spot Lesions

What other literature exists?

- RCT’s
- SR’s
- MA’s

Studies on ProSeal since 2004

- 5 in vitro studies: ProSeal decreases demineralization
- 1 in vivo study (2-month duration): ProSeal decreases demineralization (Shinaishin, et al. 2011)
- 1 in vivo “alternating tooth” study (12 – 18 months): ProSeal no better than Control (Leizer, et al. 2010)
- Which is most convincing?

Leizer, et al. 2010

- In vivo
- Observation time similar to treatment time
- Cross-over effect?

Fluoride-containing orthodontic adhesives and decalcification in patients with fixed appliances: a systematic review

- 5 RCTs and 5 Clinical Trials met inclusion criteria
- Glass ionomer better than resin adhesive, but had more debonds during treatment
- Unclear which resin adhesives are effective in prevention

An update of the 2004 Cochrane Review was performed in 2013
White Spot Lesions

**Fluorides for the prevention of early tooth decay (demineralised white lesions) during fixed brace treatment.**
Benson PE², Parkin N, Dyer F, Millet DT, Fumese S, Germain P.

- 14 of 15 prior studies disqualified
  - 5 quasi-randomization
  - 5 split mouth design
  - 3 used extracted teeth
  - 1 used same intervention

- 3 studies qualified for updated review
  - Study with lowest risk of bias found fluoride varnish was effective (application every 6 weeks led to 70% reduction in WSL)
  - One study found no difference between different F1 toothpaste/mouthwash regimens
  - One study judged to have high risk of bias due to high loss to follow-up (F1 bead vs F1 rinse)

**Other RCTs and SRs since 2013**
- 17 RCTs and 3 SRs on prevention of WSL
  - In general, fluoride helps
  - Sealants do not show much effect
  - 1.23% APF every 2 months may help
  - Some outcomes are more clinically relevant than others, eg, visual appearance vs bacterial counts or fluorescence measures
- 5 RCTs and 5 SR on treatment of WSL
  - Will discuss these later

Despite lots of effort, prevention has been challenging

**And when prevention fails …**
- Remineralization of affected enamel (fluoride, MI Paste)
- Removal of affected enamel (abrasion)
- Modifying surrounding enamel (bleaching)
- Restoring affected enamel (composite, veneers)

**Fluoride**
- Commonly prescribed
- Can remineralize incipient carious lesions.
- Dosage of fluoride is controversial
  - High levels remineralize only surface enamel (?)
  - Deeper layers remain demineralized (?)
- May not have good esthetic outcome
- The majority of the studies on fluoride have been in vitro or in situ, which do not necessarily simulate the conditions present in the oral cavity.
White Spot Lesions

**CPP-ACP**
- Casein Phosphopeptide-Amorphous Calcium Phosphate
- Commonly marketed for remineralization
- Sold in USA as MI Paste and in Asia and Europe as Tooth Mousse
- One formulation adds 900 ppm fluoride (MI Paste Plus or Tooth Mousse Plus)

**CPP-ACP**
- Stabilizes calcium, phosphate, and fluoride ions
- *In vitro* and *in situ* studies:
  - Deeper remineralization
  - Synergistic effect of Fluoride + CPP-ACP
- Clinical studies
  - Varied results for effectiveness of CPP-ACP

**Study Setting**
- 21 orthodontic and dental offices in Washington, Oregon, Idaho, Montana, and Utah
- Launched April 2010

**Can we remineralize WSLs *in vivo*?**

**Overall Study Design**
Single-blind RCT w/ 3 arms:
- MI Paste Plus + Oral Home Care
  - 10% CPP-ACP + 900 ppm F
  - 8 week supply applied 2x/day at home
- PreviDent fluoride varnish + Oral Home Care
  - 5% NaF (22,600 ppm F⁻)
  - Single application applied in-office
- Oral Home Care only
  - OHI + Toothpaste (~1000 ppm F⁻) + Toothbrush + Floss

**Patient Sample**
- Inclusion Criteria
  - Completed fixed orthodontic treatment less than 2 years prior to enrollment
  - 1 or more WSL on the facial surface of a Maxillary incisor that was not present prior to orthodontic treatment
  - 12 to 20 years of age

**All groups assessed 8 weeks after enrollment**
White Spot Lesions

**Patient Sample**

Target enrollment:
- **Stratum 1:** < 2 months since Deband
  - 40 patients per group
  - 120 patients total
- **Stratum 2:** > 2 months since Deband
  - 40 patients per group
  - 120 patients total

**And one more thing …**

- Interventions not started on day of deband, but several days later
- Allowed rehydration of enamel and resolution of gingival inflammation
- Photos were taken on day of deband, and day intervention began
- Allowed assessment of short-term changes prior to intervention

**Outcomes**

Improvement in white spot lesions from baseline (T1) to 8 weeks (T2), using both subjective and objective assessments.

**Self Assessment**

- Same 100 mm Visual Analog Scale (VAS)
  - 0 mm = ‘no improvement or worsened’
  - 100 mm = ‘white spot(s) completely disappeared’
- No before photographs shown

**Assessment for our study**

- For panels, median values used from each subject to calculate overall mean improvement
- Average values used for self-assessment
- Objective Assessment - % change in area of WSL

**Overall Enrollment**

- < 2 month stratum
  - 115 completed study
- > 2 month stratum
  - 25 completed study
- T0 - T1 group
  - Data for 34 subjects
- Results from < 2 month stratum first
Subject Flow Chart (< 2 month stratum)

- Randomized (n=135)
- Allocation
  - MI Paste Plus
    - n=45
  - Fluoride Varnish
    - n=42
  - Home Care
    - n=48
- 8-week period
- Lost to follow-up
  - MI Paste Plus: n=11
  - Fluoride Varnish: n=2
  - Home Care: n=7
- Final analyses
  - MI Paste Plus: n=34
  - Fluoride Varnish: n=40
  - Home Care: n=41

Baseline characteristics among 3 groups

<table>
<thead>
<tr>
<th></th>
<th>MI Paste Plus</th>
<th>Treatment Group</th>
<th>MI Paste Plus</th>
<th>Treatment Group</th>
<th>MI Paste Plus</th>
<th>Treatment Group</th>
<th>MI Paste Plus</th>
<th>Treatment Group</th>
<th>MI Paste Plus</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>14.6 (1.4)</td>
<td>14.4 (1.5)</td>
<td>14.6 (1.4)</td>
<td>14.4 (1.5)</td>
<td>14.6 (1.4)</td>
<td>14.4 (1.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Gender</td>
<td>Male 49 %</td>
<td>50 %</td>
<td>Male 49 %</td>
<td>50 %</td>
<td>Male 49 %</td>
<td>50 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race or ethnicity</td>
<td>Non-Hispanic white 19 %</td>
<td>23 (13 %)</td>
<td>23 (13 %)</td>
<td>Non-Hispanic white 19 %</td>
<td>23 (13 %)</td>
<td>23 (13 %)</td>
<td>Non-Hispanic white 19 %</td>
<td>23 (13 %)</td>
<td>23 (13 %)</td>
<td>Non-Hispanic white 19 %</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>Unreported 9 (26 %)</td>
<td>14 (35 %)</td>
<td>13 (35 %)</td>
<td>Unreported 9 (26 %)</td>
<td>14 (35 %)</td>
<td>13 (35 %)</td>
<td>Unreported 9 (26 %)</td>
<td>14 (35 %)</td>
<td>13 (35 %)</td>
<td>Unreported 9 (26 %)</td>
</tr>
<tr>
<td>Number of teeth affected</td>
<td>MI Paste Plus     2.3 (1.0)</td>
<td>2.2 (1.0)</td>
<td>2.2 (1.0)</td>
<td>MI Paste Plus     2.3 (1.0)</td>
<td>2.2 (1.0)</td>
<td>2.2 (1.0)</td>
<td>MI Paste Plus     2.3 (1.0)</td>
<td>2.2 (1.0)</td>
<td>2.2 (1.0)</td>
<td></td>
</tr>
<tr>
<td>% Surface area affected</td>
<td>MI Paste Plus     11.8 (8.6)</td>
<td>11.5 (8.6)</td>
<td>11.8 (8.6)</td>
<td>MI Paste Plus     11.8 (8.6)</td>
<td>11.5 (8.6)</td>
<td>11.8 (8.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral hygiene level (%)</td>
<td>MI Paste Plus     3 (65 %)</td>
<td>2 (37 %)</td>
<td>2 (37 %)</td>
<td>MI Paste Plus     3 (65 %)</td>
<td>2 (37 %)</td>
<td>2 (37 %)</td>
<td>MI Paste Plus     3 (65 %)</td>
<td>2 (37 %)</td>
<td>2 (37 %)</td>
<td></td>
</tr>
<tr>
<td>Flossing (%)</td>
<td>MI Paste Plus     14 (44 %)</td>
<td>16 (44 %)</td>
<td>14 (44 %)</td>
<td>MI Paste Plus     14 (44 %)</td>
<td>16 (44 %)</td>
<td>14 (44 %)</td>
<td>MI Paste Plus     14 (44 %)</td>
<td>16 (44 %)</td>
<td>14 (44 %)</td>
<td></td>
</tr>
<tr>
<td>% Private</td>
<td>MI Paste Plus     86 (107 %)</td>
<td>90 (114 %)</td>
<td>88 (107 %)</td>
<td>MI Paste Plus     86 (107 %)</td>
<td>90 (114 %)</td>
<td>88 (107 %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sore from orthodontic</td>
<td>MI Paste Plus     1.0 (1.8)</td>
<td>0.0 (1.7)</td>
<td>1.0 (2.1)</td>
<td>MI Paste Plus     1.0 (1.8)</td>
<td>0.0 (1.7)</td>
<td>1.0 (2.1)</td>
<td>MI Paste Plus     1.0 (1.8)</td>
<td>0.0 (1.7)</td>
<td>1.0 (2.1)</td>
<td></td>
</tr>
<tr>
<td>appliance removal (%)</td>
<td>MI Paste Plus     24 (71 %)</td>
<td>31 (78 %)</td>
<td>27 (78 %)</td>
<td>MI Paste Plus     24 (71 %)</td>
<td>31 (78 %)</td>
<td>27 (78 %)</td>
<td>MI Paste Plus     24 (71 %)</td>
<td>31 (78 %)</td>
<td>27 (78 %)</td>
<td></td>
</tr>
<tr>
<td>% Hot water</td>
<td>MI Paste Plus     9.3 (4.8)</td>
<td>9.6 (3.5)</td>
<td>11.0 (6.8)</td>
<td>MI Paste Plus     9.3 (4.8)</td>
<td>9.6 (3.5)</td>
<td>11.0 (6.8)</td>
<td>MI Paste Plus     9.3 (4.8)</td>
<td>9.6 (3.5)</td>
<td>11.0 (6.8)</td>
<td></td>
</tr>
</tbody>
</table>

Important

- Baseline characteristics not different
- Number of teeth affected and severity of lesion not different
- About 50% had poor OH in all 3 groups
- Time since debanding and follow-up time not different

Results

No difference among the study arms!

Some examples from the < 2 month stratum

Data from > 2 month stratum
Subject Flow Chart

- Randomized (n=35)
  - Allocation
    - MI Paste Plus (n=12)
    - Fluoride Varnish (n=12)
    - Home Care (n=11)

8-week period
- Lost to follow-up (n=5)
- Lost to follow-up (n=3)
- Lost to follow-up (n=2)

Final analyses
- n=7
- n=9
- n=9

Results (> 2 month stratum)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>MI Paste Plus (n=7)</th>
<th>PreviDent® Fluoride Varnish (n=9)</th>
<th>Normal home care (n=9)</th>
<th>All (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Expert Panel</td>
<td>11.0</td>
<td>12.1</td>
<td>9.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Lay Panel</td>
<td>12.6</td>
<td>15.5</td>
<td>10.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Objective</td>
<td>0.84</td>
<td>7.9</td>
<td>0.12</td>
<td>13.6</td>
</tr>
<tr>
<td>Self assessed</td>
<td>47.9</td>
<td>10.1</td>
<td>40.1</td>
<td>24.2</td>
</tr>
</tbody>
</table>

T0 - T1 (no treatment)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert Panel (n=34)</td>
<td>25.3</td>
<td>24.4</td>
</tr>
<tr>
<td>Lay Panel (n=34)</td>
<td>28.2</td>
<td>24.7</td>
</tr>
</tbody>
</table>

Some examples from the > 2 month stratum

Summary of Current study

- MI Paste Plus or PreviDent varnish not more effective than home care over 8 week period for improving the appearance of WSL
- Less improvement seen when time since debanding is greater 2 months
- Some spontaneous improvement during 1st week

Hierarchy of Evidence

- Data Synthesis
- Experimental Studies
- Observational Studies
- Anecdotal Information

http://www.cebm.net/levels_of_evidence.asp
White Spot Lesions

Discussion

- Strengths
  - Objective and subjective scores in agreement
  - Multi-site study improves generalizability
  - Patient characteristics similar at onset

Other RCT’s & SRs on Treating WSL

- 5 RCT’s since 2013
- 5 SR’s since 2013
- What to they report?

Systematic Reviews

- Chen, et al. 2013: “…lack of reliable evidence to support the effectiveness of remineralization agents”
- Sonesson, et al. 2017: “There is a lack of reliable scientific evidence to support re-mineralizing or camouflaging strategies to manage post-orthodontic white spot lesions.”
- Lopateine, et al. 2016: “…usage of fluoride and casein supplements in ameliorating WSL is effective…”
- Paula, et al. 2016: Studies are inconclusive

What other evidence exists?

RCT’s

- Agarwal, et al, 2013: Fl toothpaste led to improvement in MN but not MX teeth, compared to non-Fl toothpaste
- He, et al. 2016: Fl varnish and Fl film may be better than control, but used QLF
- Singh, et al. 2016: Varnish, MI Paste no better than routine brushing
- Bock, et al. 2017: no difference with 1.25% Fl gel
- Ebrahimi, et al. 2017: MI Paste, Remin Pro, 2% FL better than control (10 day study)

IF THESE 3 ARMS ARE EQUAL, DOES SOMETHING ELSE AFFECT IMPROVEMENT?
White Spot Lesions

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**Compliance with MI Paste Plus (experts)**

- Improvement ratings (experts)
- Times per day X days per week

---

**Subjective** = Visual Analog Scale by “Expert Panel”

**Objective** = Surface Area Change

**Improvement Scale = Rate 1-5**
1. Significantly Worse
2. Slightly Worse
3. Same
4. Slightly Better
5. Significantly Better

---

**Evaluation Level**
- Evaluation Type
- Outcome Measures
- Factors Evaluated
  - Age
  - Gender
  - Time since deband
  - Brushing frequency
  - Oral hygiene
  - Retainer type
  - Initial WSL Surface Area

**Single Teeth Improvement Scale**
1. Significantly Worse
2. Slightly Worse
3. Same
4. Slightly Better
5. Significantly Better

---

**Tooth Thirds Improvement Scale**
1. Significantly Worse
2. Slightly Worse
3. Same
4. Slightly Better
5. Significantly Better

**Statistical Analyses**

- **Linear Regression**
  - Univariate Analysis
  - Multivariate Analysis
  - Adjusted for treatment arm

- **Generalized Estimating Equations**
  - Clustering by site
  - Clustering by patient

---

**Diffuse lesion**

**Discrete lesion**

**Mixed lesion**

---

**Table: Tooth Thirds (N=738)**

<table>
<thead>
<tr>
<th>Location</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gingival</td>
<td>320</td>
<td>44%</td>
</tr>
<tr>
<td>Middle</td>
<td>331</td>
<td>46%</td>
</tr>
<tr>
<td>Incisal</td>
<td>77</td>
<td>11%</td>
</tr>
</tbody>
</table>

**Lesion Quality**

- **Diffuse**: 640 (88%)
- **Discrete**: 50 (7%)
- **Mixed**: 38 (5%)
### WHAT PATIENT FACTORS AFFECTED IMPROVEMENT?

- **AGE**: (Older, more improvement)
- **GENDER**
- **TIME SINCE APPLIANCE REMOVAL**: (Longer, less improvement)
- **LENGTH OF TREATMENT**: (More, better)
- **TOOTH BRUSHING FREQUENCY**
- **ORAL HYGIENE**
- **RETAINER TYPE**

### WHAT TOOTH FACTORS AFFECTED IMPROVEMENT?

- **INITIAL SURFACE AREA**: (Larger, more improvement)
- **TOOTH TYPE**: (Centrals better than laterals)
- **STAINING**
- **LOCATION**
- **DIFFUSENESS**

**Time since deband best predictor, Less time = better improvement !**

### In vivo challenges

- Patients were/are poor compliers
- Penetration through plaque
- Sporadic or short application
- In vivo lesions are usually deeper
- Depth may affect improvement ?
- In vivo lesions have fluoride-rich surface layer

### In-office protocol for MI Paste Plus

- **Etch**: 15 - 60 seconds with 37% H3PO4
- **Microabrasion (optional)**: pumice up to 30 sec
- **MI Paste Plus**: Apply for minimum of 5 min
- **No food or drink for 30 min**
- **Follow-up at home**: 5 min twice a day