Novel therapies for HPV-related anal disease

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Increasing Age in HIV

HPV associated Anal Cancer Incidence
In MSM per 100,000 py

Low nadir CD4, alcohol use, and smoking are significantly associated with anal cancer in HIV+ MSM

Cervical cancer
Anal Cancer

CIN = Anal Intraepithelial Neoplasia
AIN = Anal Intraepithelial Neoplasia
HPV = Human Papillomavirus
Mucosal transformation zone
Precancerous lesions

FIGURE 1: Anal cancer incidence per 100,000 person-years (with 95% CI) for 9 consecutive 2-year blocks in all HIV-patients and HIV+ MSM separately in the Netherlands (1995–2012).
AIN progression

AIN prevalence

- AIN prevalence in HIV+ MSM: 50-80%
- High Grade (HG) AIN: 30-50%

AIN screening?

Treatment of AIN

- Hardly any prospective studies
- Ablation via heat coagulation is the standard treatment option
  - Suboptimal response rates
  - Recurrence rate is high
- Alternative ablative therapies:
  - Trichloroacetic acid (TCA)
  - Liquid nitrogen
- Alternative non-ablative therapies
  - Imiquimod (TLR-9 agonist, IFN-gamma inducer)
  - 5-fluorouracil (cytostatic)

Triple arm trial in 146 HIV+ MSM

- Screening by high resolution anoscopy
- Histopathologically proven AIN
- Randomisation:
  - 16 wks imiquimod 3 times a week
    - patient administered
  - 16 wks topical 5-fluorouracil twice a week
    - patient administered
  - 16 wks of monthly electrocautery (up to 5 sessions)
    - provider administered

Response Rate

Response for peri-anal and intra-anal lesions separately

Richel et al 2013 Lancet Oncol
Cumulative recurrence

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Imiquimod</th>
<th>Fluorouracil</th>
<th>Electrocautery</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>27% (13/48)</td>
<td>19% (7/37)</td>
<td>38% (9/24)</td>
<td>54% (21/39)</td>
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<td>48 weeks</td>
<td>46% (22/48)</td>
<td>47% (7/15)</td>
<td>50% (6/12)</td>
<td>43% (4/9)</td>
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<tr>
<td>57 weeks</td>
<td>55% (30/45)</td>
<td>77% (10/14)</td>
<td>50% (2/12)</td>
<td>68% (13/19)</td>
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</table>

Data are % (n/N) Cumulative recurrence rates at weeks 24, 48, and 52 after treatment. Of the 54 patients initially responding to treatment, 30 patients returned for a follow-up high-resolution anoscopy 24 weeks after treatment. An additional two and three patients were lost to follow up at the 48-week and 22-week visits.

Table 3 Cumulative recurrence rates

Richel et al 2013 Lancet Oncol

**Conclusion**

Electrocautery is more effective than imiquimod and 5-FU for the treatment of intra anal AIN, but all have high recurrence rates.

Imiquimod seems to be treatment of choice for peri-anal AIN.

Electrocautery shows milder and shorter lasting side effects.

HGAIN, years on ART and high CD4 count are related to treatment success.

**Quadrivalent HPV Vaccination After Effective Treatment of Anal Intraepithelial Neoplasia in HIV+ Men (VACCAIN-P)**

- Goldstone et al 2012: open study 202 patients treated for HGAIN
  - 88 vaccinated: 13.6% recurrent HGAIN
  - 114 unvaccinated: 30.7% recurrent HGAIN

- Vaccination with quadrivalent HPV vaccine versus placebo on prevention of high grade AIN recurrence in HIV-positive MSM who were successfully treated for high grade AIN.

- Multicenter, randomised, double-blind clinical trial in 4 hospitals in the Netherlands (n=200).

- Primary end point will be the cumulative recurrence of HG AIN at 12 months after the last vaccination, as assessed by HRA (High-Resolution Anoscopy), with biopsies taken of suspect lesions.

**Therapeutic vaccine using E7 protein as target**

- HspE7: fusion of the human papillomavirus (HPV) 16 E7 protein and the Mycobacterium bovis heat shock protein 65
- Phase I/II trial to study the effectiveness of HspE7
- 3 cohorts of 5 participants each, sequentially assigned to receive 100, 500 or 1000 mg HspE7, injected 3 times subcutaneously at 4-week intervals.
- HspE7 was well tolerated, no sign changes in VL or CD4 count
- 3/5 (60%) with disease regression became HPV-negative, compared with none of 10 with no clinical response ($P = 0.02$)

Palefsky, AIDS 2006

**Therapeutic HPV-16 Vaccination for the Treatment of Anal Dysplasia (VACCAIN-T)**

- Kenter et al NEJM 2009: VIN (vulvar intraepithelial neoplasia) synthetic long-peptide vaccine SLP HPV-01® (peptides from the HPV-16 viral E6 and E7)
  - Well tolerated, effective >70% HGVIN
  - Strong HPV-16-specific immune response
  - Highly efficacious

- Safety/ toxicity of the HPV-16 vaccine in HIV+ MSM
- Regression of intra-anal high grade AIN lesion
- HPV16-specific immunity in blood
  - T-cell assays: i.e. proliferation (LST), cytokine production (IFNγ, TNFa, IL-4, IL-5, IL-10, and IL-2) as well as by ELISPOT (IFNγ)

- First phase dose-response study, 3 different dosage schedules SLP-HPV-01® intradermally with a three-week interval, with or without peg IFN-α. Each vaccination n=5.

- The optimal vaccination schedule will be increased to 20 patients by treating an additional 15 patients.

Palefsky, AIDS 2006

[Image of HPV Vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia]
Ablative interventions

- Tolerability, Safety & Efficacy of Argon Plasma Coagulation for AIN in HIV+ Men
  - Phase II, Prospective, Open-label, Pilot Study, n=20
  - Alexandre de Polonovski, Centre hospitalier de l’Université de Montréal (CHUM), Canada
  - Recruitment closed awaiting results

- The HPV-SAVE Study Team: HPV Screening and Vaccine Evaluation in MSM
  - Ablative therapy involving either inframes coagulation (IRC) or electrocautery (EC)
  - The control arm includes active surveillance with observation alone
  - Irving Salt, University Health Network, Toronto
  - Not yet recruiting

- A Safety and Tolerability of Circumferential Anal Canal Radiofrequency Ablation for Anal Intraepithelial Neoplasia
  - Open-label
  - Radiofrequency Ablation circumferential radiofrequency ablation (RFA) to the anal canal
  - Sponsor: Medtronic
  - Ongoing

Other interventions

- Treatment of Anal HSIL with a Chinese Herbal Topical Cream
  - Placebo controlled
  - Arnebia Indigo Jade Pearl Cream 1/4 teaspoon twice daily for 48 weeks.
  - Misha K Cohen, UCSF School of Nursing
  - Ongoing

- Chemoprevention of AIN in Persons With HIV Infection.
  - To evaluate the effects of isotretinoin alone or in combination with IFN alfa-2a on immune function markers, human papillomavirus (HPV) type, and HPV DNA levels
  - Phase I and II (after ablation)
  - Palefsky JM in collaboration with Hofmann-La Roche
  - Completed, awaiting results

- CIDOFVIR 1%, 3 Nights Per Week, During 4 Weeks, of Anal Intraepithelial Neoplasia, High Level, in HIV+ Patients (632AN12)
  - Open-label
  - Elena Sendagorta, MD Hospital La Paz, Madrid, Spain
  - Ongoing

Conclusions

- Little evidence based data on the treatment of AIN in HIV+ MSM
  - Electrocoagulation is the recommended treatment option
  - Urgent need for high quality RCT’s

- Most currently available treatment options show disappointing outcome results and high recurrence rates
  - Makes screening HIV+ MSM for AIN less effective

- Inducing an effective immune response via therapeutic vaccination might be more promising than ablative treatment options

- Universal prophylactic HPV vaccination for could eliminate anal cancer on the longer term

Large observational study

- ANCHOR Study: Anal Cancer/HSIL Outcomes Research Study
  - Topical or Ablative Treatment in Preventing Anal Cancer in Patients With HIV and Anal High-Grade Squamous Intraepithelial Lesions
  - Randomized phase III trial compares topical or ablative treatment with active monitoring in preventing anal cancer in HIV+ patients with high-grade squamous intraepithelial lesions (HSIL).
  - Recruiting (n=5058) expected completion 2022
  - Joel Palefsky, MD AIDS Associated Malignancies Clinical Trials Consortium

AIN in Amsterdam

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