Evaluation of Different Treg Depletion Approaches as Strategies for Improved SIV Reactivation and Clearance

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BACKGROUND

• T regulatory cells (Tregs) can be latently infected with HIV and may represent a potentially important HIV reservoir
• They expand in blood and tissues in chronically HIV-infected patients and SIV-infected macaques\(^1\)
• HIV/SIV DNA positive cells are more abundant in Tregs than in non-Tregs in patients on ART and in rhesus macaques (RMs)\(^2,3\)
• Tregs are less susceptible to cell death than conventional T cells

BACKGROUND

- T regulatory cells (Tregs) have a critical contribution to the shape of the viral reservoir
- During acute infection, Tregs decisively contribute to the establishment of HIV reservoir by reversing CD4+ T cell immune activation status
- During chronic infection, Tregs contribute to the impairment of CTL responses, as their expansion correlates with loss of CTL function and their ex vivo depletion enhances T cell responses to HIV/SIV antigens.
- The HIV-specific CD8+ T cells from elite controllers evade Treg suppression
BACKGROUND

• These observations support a major involvement of Tregs in suppressing protective effector immune responses against HIV

• This Treg effect may be critical for the “shock and kill” strategies, which require increased virus killing of the reactivated virus
HYPOTHESIS

Treg depletion is a valid HIV cure approach, as through a single intervention we can

• reduce the size of the reservoir
• reactivate the virus
• boost cell-mediated immune responses
RATIONALES for the different therapeutic interventions aimed at Treg depletion

<table>
<thead>
<tr>
<th>Anti-CCR4 DT</th>
<th>IL2 DT</th>
<th>Combination DT</th>
<th>Cyclophosphamide</th>
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<tbody>
<tr>
<td>High concentrations of CCR4 are present on the surface of Tregs, which make CCR4 a plausible target for Treg depletion.¹</td>
<td>The IL-2 receptor is CD25, which is a surface marker of Tregs. As such, CD25 is a plausible target for Treg depletion.²</td>
<td>A combination of the anti-CCR4 DT and the IL2 DT could improve the efficacy of Treg depletion (which is needed as Fox-P3 cannot be directly targeted being an intracellular marker).</td>
<td>Low doses of Cyclophosphamide have been shown to selectively deplete Tregs, although the mechanism is poorly understood.³</td>
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Treg Depletion

Anti-CCR4 DT

IL2-DT

Combination DT

Cyclophosphamide

Blood

SLN

Gut
Total Lymphocytes

CD4+ T-Lymphocytes

Anti-CCR4DT

IL2-DT

Combination DT

Cyclophosphamide

Blood

Blood

Gut

CD4+ cells/μL

CD4+ cells (%)

Days Post Treatment

Days Post Treatment

Days Post Treatment

Days Post Treatment

Days Post Treatment

Rx

Rx

Rx

Rx

Rx

Rx
Immune Activation

Anti-CCR4DT  IL2-DT  Combination DT  Cyclophosphamide
Plasma Viral Loads

Anti-CCR4DT | IL2-DT | Combination DT | Cyclophosphamide

Days Post Treatment | Days Post Treatment | Days Post Treatment | Days Post Treatment

vRNA copies/mL

Rx

RM39 | RM40 | RM73

RM39 | RM40 | RM246 | RM247 | RM73 | RM250

RM96-16 | RM97-16 | RM98-16

RM39 | RM40 | RM73
CONCLUSIONS

• Cy proved to be an effective cytoreductive agent and its impact on the reservoir has to be investigated.

• Immunotoxin therapies were relatively similarly effective in depleting Tregs, yet virus reactivation and the boost of SIV-specific immune responses were more prominent after IL2-DT, probably due to the IL-2-induced activation or to the loss of suppressing abilities of residual Tregs after IL2-DT-treatment.

• Treg depletion boosted CTLs, clearing the reactivated virus.
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