

## BMS-663068, a safe and effective HIV-1 attachment inhibitor

The entry of HIV into target cells is a multistep process involving viral attachment, coreceptor binding, and fusion. Although various inhibitors targeting HIV-1 entry steps have been developed, only maraviroc, a CCR5 antagonist, and enfuvirtide, a fusion inhibitor, are approved for clinical use.<sup>1</sup> Attachment inhibitors prevent the initial interaction between virus and host cells by binding to the viral envelope protein gp120 and blocking attachment of the virus to the CD4 receptor. Attempts to bring attachment inhibitors to the clinic did not progress.<sup>2</sup> However, an effort to increase the inhibitory potency of attachment inhibitors led to the discovery of BMS-626529 (the first in a new class of these drugs)<sup>3</sup> and its prodrug BMS-663068, which has better solubility and pharmacokinetic profile.<sup>4</sup>

In *The Lancet HIV*, Jacob P Lalezari and colleagues<sup>5</sup> report the primary results of the phase 2b trial of BMS-663068. Proof of concept for the class of attachment inhibitors was achieved in an 8 day monotherapy trial of the progenitor BMS-488043.<sup>6</sup> BMS-663068 showed similar efficacy to a boosted protease inhibitor (atazanavir plus ritonavir reference group) in combination antiretroviral therapy (cART), without the appearance of important adverse effects. The antiretroviral activity of BMS-663068 was confirmed in a monotherapy substudy.<sup>5</sup> The initial endpoint analysis of phase 2b trial showed promising results that warrant further development of BMS-663068 and eventually other attachment inhibitors.

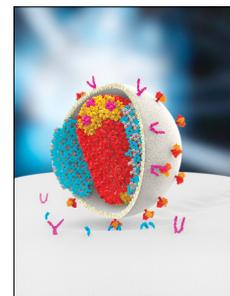
One of the strengths of the trial was the possibility of assessing safety and efficacy in a substantial number of patients, resembling the final target population (ie, heavily treated patients with extensive drug resistance requiring an alternative rescue therapy with a novel mode of action). Patients enrolled in the BMS-663068 trial were all treatment-experienced but mostly reflecting first-line or second-line virological failure, which might not be the population intended for treatment with a salvage therapy. Thus, the efficacy of BMS-663068 in such a group of patients with limited treatment options remains to be demonstrated.

To manage the complex and highly individualised requirements of treatment-experienced patients, antiretroviral drugs must have activity against drug-resistant virus and limited or manageable drug interactions, so

they can be used effectively in combination with other antiretrovirals or concomitant medications. Up to now and probably because of the novel mechanism of action of attachment inhibitors, no relevant drug interactions have been described for BMS-626529.<sup>7,8</sup> However, and in contrast to many antiretroviral drugs, common viral subtypes show a broad range of susceptibility to BMS-626529,<sup>3</sup> an issue that might be an important roadblock for the final prescription of attachment inhibitors. On the basis of previous work, Lalezari and colleagues<sup>5</sup> did not enrol patients with a BMS-626529 half-maximum inhibitory concentration greater than 100 nmol/L at entry, representing an a priori selection that might overestimate the potency of the attachment inhibitors.

Differences in BMS-626529 susceptibility have been presumably attributed to the high level of diversity found in gp120 itself and the effect that aminoacid mutations can have on the conformational structure of the protein,<sup>9</sup> but the reality is that genotypic and phenotypic correlates of susceptibility to BMS-626529 are still rather unclear. In a monotherapy study<sup>10</sup> of patients infected with HIV-1 subtype B, correlates of non-response mapped to aminoacid changes in gp120, which were previously shown to confer resistance to BMS-626529 in cell culture.<sup>11</sup> In that study,<sup>10</sup> the envelope substitution Met426Leu was found to be strongly, although not exclusively, associated with low susceptibility to BMS-626529. Other envelope aminoacid changes that encoded reduced susceptibility to BMS-626529 in this cohort included Ser375Met/Thr, Met434Ile, and Met475Ile.<sup>11</sup> Data from the phase 2b trial<sup>5</sup> do not allow to clearly solve this issue, albeit a group of patients at least developed a resistance phenotype. A longer and deeper analysis of this samples might help unravel the existence or not of resistance mutations.

In summary, the study from Lalezari and colleagues<sup>5</sup> explores the efficacy of an attachment inhibitor as part of cART with promising results, but some issues are unresolved. Further work must determine efficacy and effectiveness in heavily treated patients with limited treatment options. Moreover, since a clinical cutoff has not been determined, and natural envelopes with reduced sensitivity to the compound exist, a diagnostic test might be required to ensure the optimum clinical use



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Published Online  
September 2, 2015  
[http://dx.doi.org/10.1016/S2352-3018\(15\)00160-5](http://dx.doi.org/10.1016/S2352-3018(15)00160-5)  
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of BMS-663068. To achieve this goal, additional analyses are needed to better determine the correlation between genotypic envelope sequence and clinical response.

The development of attachment inhibitors is not only a need for patients receiving subsequent salvage therapy but it also could represent an improvement in the portfolio of current antiretroviral therapies. The additional potential benefits associated to the unique effect of their mechanism of action (the prevention of the initial interaction between virus and host cell) might positively affect immune restoration and ameliorate inflammation and cellular activation.

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We declare no competing interests.

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