Regulatory issues and challenges in salvage therapy

(A personal take on Panel 4. Discussion leader: Trip Gulick)

By Martin Delaney

Panel 4 focused on how regulatory issues were presently affecting options for salvage patients. Initial discussion noted that the numerous changes and improvements made at the Food and Drug Administration (FDA) over the last 20 years, often as a result of community input and pressure, have eliminated most of the regulatory obstacles that once existed. In short, today the FDA is not perceived as a major roadblock to the development of salvage therapy.

Nevertheless, the participants of the group pointed out that this did not mean that people requiring true salvage therapy could always get what they needed. One of the biggest problems in the realm of salvage therapy is that it is seldom possible to obtain access to more than one new drug at any particular time. Yet we know that simply bringing in one effective drug, when a person is failing all available drugs and combinations, provides little more than short-term improvement. The addition of a single new drug in a salvage setting is basically equivalent to monotherapy and, with the drugs presently available, it is all but impossible to achieve a lasting and powerful antiviral response with a single drug. The necessity of effective combination therapy is even more critical in the salvage setting than it is for people initiating antiretroviral therapy.

Some of the clinicians in the discussion group commented that even "failing" drugs often provide a degree of viral suppression. One reason for this is that the drug-resistance mutations that develop and cause a drug to "fail" also may cause it to replicate less effectively. New diagnostic tests that measure the replicative capacity of a person's virus are currently being studied to help quantify and characterize this effect. Nonetheless, the most desirable situation is for the person in a salvage situation to have access to at least 2 new active drugs at the same time.

Several obstacles make this scenario difficult to achieve. One major factor is that multiple new drugs rarely, if ever, come from the same company. If a single company is developing 2 antiretroviral agents, they are usually not in the same stage of development because each drug moves forward at its own pace. Although different companies have historically shown little or no willingness to make their individual drugs available under a common timeline, the FDA has stated that it does not oppose study designs that include 2 or more investigational new drugs. Community pressure regarding these issues therefore needs to be directed, not at the FDA, but at the individual companies developing the drugs.

For example, Tibotec has 2 drugs in parallel development, a protease inhibitor (PI) with good activity against PI-resistant virus and a new non-nucleoside reverse transcriptase inhibitor (NNRTI) that over-

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comes viral resistance to other drugs of this type. Both community advocates and scientists agreed that the situation developing at Tibotec was especially well suited to test an approach studying 2 investigational agents in one study. Developing clinical trials that allow people access to these 2 new drugs at the same time should be relatively simple. In addition, tipranavir, a protease inhibitor developed by Boehringer Ingelheim, will be also accessible in this time frame. Farther down the road, at least 2 new entry inhibitor drugs will most likely become available at a similar time. Thus, the prospects for treating people in need of salvage therapy with 2 or more new drugs at the same time appear quite good.

This issue of multi-drug availability also pertains to expanded access (EA) programs. Almost every drug has an EA program that makes the drug available to people in need before formal FDA approval. The challenge for salvage therapy is to coordinate 2 or more such programs so that salvage patients have access to 2 or more new drugs at the same time. Again, this issue is not so much a regulatory issue as it is a "collaboration" issue between pharmaceutical companies. Community pressure must be placed on the individual companies to coordinate their EA programs. While such coordination may be challenging, there is no inherent reason why this cannot be achieved.

Some advocacy representatives commented that even if EA programs could be coordinated, and some studies combined 2 or more new drugs, there would still be patients who could not obtain access to multiple new agents at the same time. Not all people are qualified for these clinical trials, nor do they all live in locations served by the trials. Furthermore, there will always be people who need access to multiple new drugs prior to the launch of EA programs. This highlights the dilemma of a number of people in the salvage setting and asks the question "how can we provide these patients with the necessary access to multiple new drugs at the same time?"

At the Salvage Therapy meeting, researchers and community activists alike found this to be the most challenging situation. Fortunately, this dilemma is not that common. One possible approach is the use of a mechanism that would provide access to the needed new drugs on a "case by case" basis (sometimes called "compassionate use"). Some of the clinicians, however, feared it would require a great deal of paperwork on their part for each patient. In response, community advocates pointed out that the monumental paperwork procedures were not necessarily required and instead a bad habit of the FDA and pharmaceutical companies. Individual access should be achievable with minimal paperwork as long as the manufacturers and the FDA are committed to making it happen.

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