Ad Fib

The nelfinavir “Maximize Your Options” line

January 1, 1998 By Mike Barr

When it comes to positioning for the protease-inhibitor market share, every drug maker has a yarn to spin. Since the buzz on the street by 1996 was that Agouron Pharmaceuticals’ still-unlicensed nelfinavir (Viracept) was likely less potent than its competitors, the company decided to have a go at the “unique resistance pattern” angle. By then it was also clear that these “miracle” drugs shared such complete cross-resistance that people with HIV faced an apocalyptic scenario: Your first protease isn’t only your best shot – it’s very likely your last. Nelfinavir, the glossy two-page ads promised, was different: With this late-comer protease you could “Maximize Your Treatment Options.”

In fact, early test-tube experiments did show nelfinavir to be blessed with an idiosyncratic mix of mutations. If Agouron’s resistance luck held, the tiny startup would find itself sitting on a veritable gold mine: Filling nelfinavir prescriptions – either as a first-line treatment or after other protease inhibitors failed – for virtually every person with HIV. The company’s virologist-for-hire, Amy Patick, was duly dispatched to scientific meetings, where she tonelessly called out the mutations – D30, G88, I77 – as if in a bingo hall. But Agouron scientists were already well aware that the “unique” mutations were only the first step to develop and were fast followed by others, including the usual suspects – 90, 84 and 71 – that would make the virus insensitive to other protease inhibitors. The only question for Agouron (and its stock-holders) was: How long could the troubling truth be contained?

It scared (and infuriated) me to see yet another drug outfit fooling patients and doctors and feeding both a false sense of security. The obvious next step was to study what actually happens in people after nelfinavir fails and they switch to another protease-based regimen. But who would do it? For Agouron execs to initiate such a study would be financial suicide. Meantime, the federal clinical-trials network was wrapped up in Dr. Doug Richman’s one-year-to-eradication-or-bust protocol and wrangling over Dr. Mike Saag’s perfect-strategy study; community-based docs weren’t up for research unattached to a funding stream; and private physicians had been up to their stethoscopes in patient visits ever since Dr. Joep Lange and Dr. David Ho first engineered the eradication hysteria to help launch a new medical journal and lure a new benefactor, respectively. If a nelfinavir-switch study was to happen, it had to come from the grass-roots.

As a site for two earlier nelfinavir studies, New York City’s St. Vincent’s Hospital (where I work) had dozens of patients, 15 or so who’d already developed resistance and switched to nevirapine or a

second protease combo. There was another site across town at Bellevue, and a third up at Bronx Lebanon. So it was straightforward enough: Call up the investigators; fax around a concept sheet; beg a little; promise to make the data-collection form user-friendly – and soon we'd have a bank of useful data. Or so it seemed. Early enthusiasm from bleary-eyed primary-care providers and lecture-circuit most-wanteds quickly faded into best-wishes kiss-offs. To further erode the odds of collecting sufficient data from the other 25-plus sites, Agouron, upon getting wind of our homespun research, threw together its own study, offering $500 for each form filled out and – strangely – asking for follow-up data on only certain hand-picked patients (those exhibiting the unique-resistance pattern?) We were way out of our league.

By the last-minute deadline for the next big-time AIDS confab, the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), we had a preliminary analysis of a mere eight patients. Still, the results were provocative: The average viral load before the switch from nelfinavir – 100,000 – had, only one month later, more than tripled, to 350,000. Only two patients had a significant post-switch viral-load reduction. Only one went "undetectable."

Surprisingly, our humble study was accepted for oral presentation at ICAAC's prestigious late-breaker session. As one of the few HIV experts on the program committee, Dr. Ho likely played a role in our paper's selection; just that week he'd publicly labeled the notion that any protease inhibitor has a unique resistance profile "a folk tale." Scientists from Merck, the maker of Crixivan (indinavir), the biggest-selling protease, could barely contain their glee; for days after the announcement, our office phone rang off the hook with Merck-ish overtures of technical assistance; we declined.

So, at midday, on September 30, in Toronto, before an audience of some 1,000 delegates, we used our allotted five minutes to show that three of our (by then) 12 study patients had responded favorably when switched from nelfinavir to a second protease-based regimen, four had a small or temporary viral-load reduction, and five had no reduction at all. Was this – a 25 percent success rate – what Agouron's crack marketing team had in mind when they coached "Maximize Your Treatment Options"?

Agouron's CEP Peter Johnson sat in the packed audience, shaking his bowed head incredulously, as media reporters and Wall Street analysts scribbled down the stats. "This is not late-breaker material," he whispered plaintively to a colleague. Later that afternoon, at an elegant dinner at the local Four Seasons Hotel, Johnson, citing the day's presentation, announced to his guests (company officers, sales reps, physician investigators and industry analysts), "We'll continue with the development of this product, taking the bad news along with the good." (He had little choice: Nelfinavir is the only licensed product in Agouron's portfolio.)

But if Johnson seemed reconciled to this downtown, high-profile New York eradication researcher Dr. Martin Markowitz was not. "I think it was outrageous," he bellowed over his pepper-crusted mahi mahi.

"It was a small, observational study, and its limitations were clearly laid out," another diner

challenged. “Everyone understood that.”

"But the *analysts* don’t,“ the eradicator said. ”Do you have any idea what this kind of a presentation will do to the company’s stock price?"

In fact, that afternoon, in New York, Agouron’s shares had closed down $5 a share – in a single day, the $92 million company had lost 10 percent of its value. At Agouron’s La Jolla, California headquarters, it was time for Operation Damage Control. Oddly enough, the following weekend, a half-page profile of the company ran in *The New York Times’* Sunday business section. A stock analyst argued that the selloff in shares had been exaggerated, and that Agouron’s prospects remained stellar. By week’s end, the share price had recovered to its pre-Toronto level – like the viral loads of many nelfinavir-resistant patients who’d banked on using a second protease. For now, the spin doctors had succeeded.

As more and more people switch after nelfinavir fails, however, doctors and other primary-care givers will develop a firsthand sense of the degree of the drug’s cross-resistance. Perhaps a quick switch to a second protease – say, within two to four weeks after the very first signs of viral rebound – will prove successful. Perhaps not. The real tragedy is that nobody knows – and Agouron has so far done nothing to guide our strategic-planning and decision-making. But if the company hopes to sustain the good will it has so ambitiously cultivated, it should focus on helping its consumers – and not simply its stock price – to do well. People with HIV deserve to know what their real treatment options truly are – and will be upon drug failure – in order to truly maximize them. It’s the least we can ask.
