

BOON OR BANE?

The benefits—and infectious complications—arising from the use of biologics

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Increasingly, the promise biologics bring to physicians and patients is being documented. This class of drug targets a particular molecular pathway to treat diseases, which makes them a better alternative to conventional therapy because of reduced side effects. Biologics are not without perils though.

“While biologics for the most part represent a considerable boon to physicians and patients alike, they are not without their own unique set of problems [that] clinicians must be aware of [so they can] utilize them with maximum benefit,” said Dr. Edsel Maurice Salvaña.

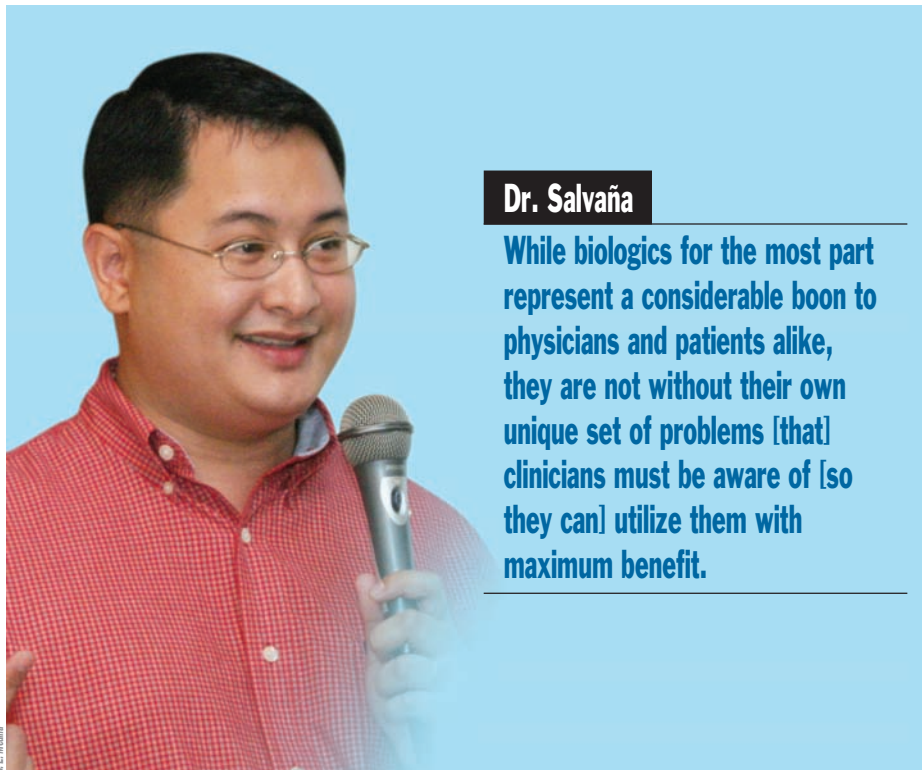
Salvaña presented a study on the “Infectious complications of monoclonal antibodies and related small molecules before the monthly research forum of the University of the Philippines–National Institutes of Health (UP–NIH).

Salvaña, who is a research faculty at the Institute of Molecular Biology and Biotechnology at the UP–NIH and associate professor at the UP College of Medicine, zeroed in on the infectious complications of monoclonal antibodies approved by the United States Food and Drug Administration.

Patients at risk

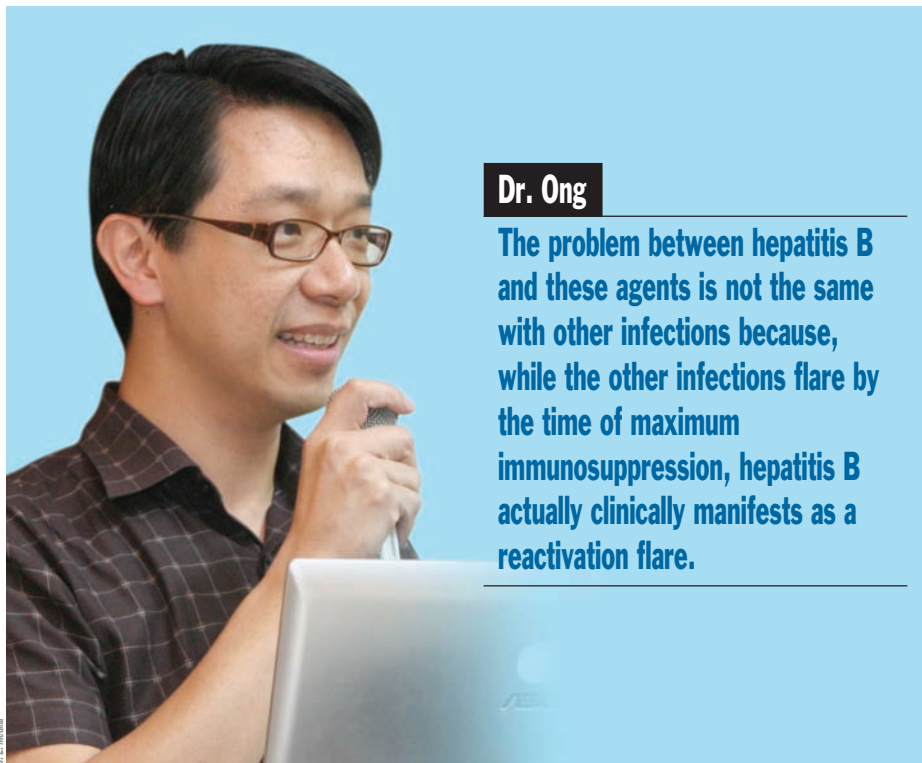
Because of their apparent benefits, biologics or “the class of drugs that includes monoclonal antibodies, receptor analogs, and chimeric small molecules” are preferred over conventional means of treatment. However, there are dangers brewing in the use of biologics as cases of both common and rare infections are rising, which Salvaña said is not at all surprising given that some agents interfere with tumor-necrosis-factor (TNF) alpha.

“While most monoclonal agents and related biologics are generally safe, a working knowledge of the infectious complications associated with these is essential [for doctors] to apprise the patient of the risks of such therapy, as well as to maintain vigilance for



Dr. Salvaña

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these adverse events,” Salvaña pointed out.

Salvaña said knowing these side effects will enable physicians to take appropriate steps to minimize infection, such as giving vaccination, testing for latent tuberculosis, and maintaining a high level of suspicion for common and unusual pathogens.

When an infection occurs, discontinuing the use of biologics remains the most reasonable option, but this isn't done so easily, Salvaña said. Patients suffering from infectious complications may require longer treatment. Because monoclonal antibodies, along with other biologics, have long half-lives, there may be a significant delay from the time patients stop using the drug to the time the immune system recovers.

In the worst-case scenario, patients may suffer from immune reconstitution, in which the immune system recovers but reacts to unrecognized antigens or substances it considers foreign. The efficient application of biologics, therefore, requires doctors to increase their understanding of the infectious complications from the use of monoclonal antibodies.

Using these agents is “not a walk in the park,” said Dr. Janus Ong, a clinical associate professor of at the UP College of Medicine, stressing they need to be used by those familiar not only with their indications, but more importantly, with their infectious side effects. “Knowing the side effects requires vigilance,” Ong said.

Targeting tuberculosis

One of the advantages of TNF-alpha inhibitors is the treatment of rheumatologic and immune-dysregulation diseases. However, TNF-alpha, which is important in forming and preserving inflammatory response against infection, increases the risk of granulomatous infections—tuberculosis specifically. To date, there are four approved TNF-alpha inhibitors: two monoclonal antibodies, one Fab fragment, and one soluble receptor.

Before treating patients with TNF-alpha inhibitors, doctors need to evaluate them for TB risk. Examinations such as tuberculin skin testing and baseline chest X-ray should be done before initiating treatment. Patients who test positive for latent TB should first be given TB chemoprophylaxis before treatment with TNF-alpha inhibitors, said Salvaña, while those who test negative should be continuously monitored. Generally, patients with active infections are advised not to use TNF-alpha inhibitors.

Ong also stressed the significance of monoclonal antibodies in relation to hepatitis B. “The problem between hepatitis B and these agents is not the same with other infections because, while the other infections

flare by the time of maximum immunosuppression, hepatitis B actually clinically manifests as a reactivation flare,” Ong explained. Such complication can kill the patient.

Attributing an infection to biologics can be difficult. “In some cases, the underlying disease process itself, along with concurrent therapy, can cause immunosuppression,” Ong explained. Immunosuppression happens in cases of autoimmune diseases, cancer, and inflammatory conditions such as rheumatoid arthritis. A definite assessment of the relationship between biologics and rare infections is also difficult to achieve because of the very low frequency. Ong asserts that the difficulty of blaming infectious risks to biologics alone is seen even in “randomized placebo-controlled trials and in large open-label studies” because of the number of confounders and the aim of the trials, which is to measure efficacy and not safety.

The future of monoclonal antibodies

To date, there are over 20 monoclonal antibodies approved for therapeutic use. The following were included in the research conducted by Dr. Salvaña: biologics for rheumatologic disease and other inflammatory conditions (adalimumab, etanercept, infliximab, and certolizumabpegol); biologics for malignancies (alemtuzumab, ibritumomab tiuxetan, and rituximab); biologics for treatment of other diseases (basiliximab, daclizumab, and muromonab); other biologics (abatecept, anakinra, riloncept, and alefacept); antimyeloid-receptor antibodies (gemtuzumab); antiangiogenesis antibodies (bevacizumab; ErbB-receptor antibodies (cetuximab, panitumumab, and trastuzumab); monoclonal antibodies for cardiovascular disease (abciximab); for neurologic disease (natalizumab); for pulmonary diseases (omalizumab and palivizumab); and for imaging (arcitumomab, technitium-fanolesomab, capromabpendetide, and nofetumomab).

“The science of monoclonal antibodies and the development of small molecules that target important cellular steps or factors, coupled with further advances in recombinant protein technology, create nearly infinite possibilities to manipulate disease pathways,” Salvaña said.

But the limitless number of challenges in using biologics remains insofar as safety is concerned. “As more and more biologics find their way into our therapeutic armamentarium, the challenge becomes not whether a drug exists to treat a disease but which is the most appropriate with the lowest number of side effects, not the least of which are infectious complications,” he summed up. **M**