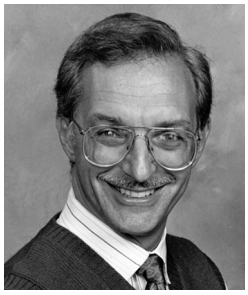
Editorial

Biologic Agents and Their Use in Resource-Poor Countries



Extensive research over the past 2 decades has led to the development of a new and exciting group of biologic therapies[1] such as tumor necrosis factor (TNF) blocking agents (adalimumab, etanercept, and infliximab). These agents have begun to revolutionize the treatment of rheumatoid arthritis and other forms of inflammatory rheumatic diseases. They are clearly very effective medications and may significantly change the course of these diseases. Not only are these agents likely to decrease the mortality of many rheumatic diseases, they will also undoubtedly improve the quality of life of treated patients. Improved quality of life and function implies increased ability to return to work and increased individual productivity. From a societal perspective, this changed productivity may conceivably translate into an increase in national productivity and income.

We suggest, in this era of biologic agents, that special considerations are necessary regarding their use in resource-poor countries (RPC). It is also appropriate to consider ways to allow the large populations of patients in RPC to have increased access to these agents.

There are special considerations and approaches that would be most appropriate regarding use of biologics in RPC, including the establishment of registries, appropriate tracking of adverse events in these countries, training in rigorous research techniques, and harmonization of outcome measures.

REGISTRIES

The extent and severity of various rheumatic diseases in RPC is not well described, much less are details known regarding their treatment. Once known, it will be much easier to define the needs of the patients in these countries and the rational treatment of their illnesses. To do this, setting up registries[2] in these countries (and appropriate controls) is in our view essential, to collate information on all patients taking a biologic agent. Without this information it will be difficult to determine the longterm safety profile of these drugs in patients outside the usual areas of their use, the resource-rich countries. As for the foreseeable future the number of patients in each RPC taking a biologic agent is likely to be small, we would suggest such registries be supported by a coalition of national rheumatic disease oriented physicians or organizations and industry. Further, as expanded below, registries of patients taking biologics may advance knowledge regarding the effects of biologics on the effectiveness of vaccinations and occurrence of lymphoproliferative diseases such as Burkitt's lymphoma (more common in some RPC). We also feel that both rheumatic disease associations and industry have important roles to play in the dissemination of information about the effectiveness, new uses, and adverse events of these biologics across RPC.

In addition to setting up registries for the biologics, we would welcome establishment of databases and toxicity registries for the traditional disease modifying antirheumatic drugs (DMARD) as controls for the biologics data, and because these more traditional drugs have been inadequately studied among populations in many RPC.

ADVERSE EFFECTS

The side effects of biologic agents remain inadequately understood particularly in RPC, where infection remains a major problem. Of course, tuberculosis is a major concern, as there has already been a resurgence of treatment-resistant tuberculosis, especially in RPC and in association with the spread of acquired immunodeficiency syndrome[2,3]. The international rheumatologic community has a role in determining and disseminating best practice with regard to screening for tuberculosis as well as understanding the interaction between biologics and other infections, including tuberculosis and tropical infections.

The issue of how biologics affect the usefulness and side effects associated with vaccinations, especially where live vaccines are used, needs further research so that firm recommendations can be made in this poorly understood area. This is particularly important in RPC, where there is a need for more widespread use of vaccinations. Similarly, whether exposure to biologics can increase the risk of developing malignancies or lymphoproliferative disorders such as Burkitt's lymphoma is not known.

RESEARCH TRAINING

To be credible, research must be held to well accepted, rig-

orous standards. And in order to contribute to and benefit from research, RPC need to develop and increase cadres of well trained researchers. In this arena, there is both a need and an opportunity. Organizations such as the World Health Organization and the International League Against Rheumatism (ILAR) can help organize courses and conferences to train such researchers[4].

OUTCOME MEASURES

There is an ongoing need for good data sets with core outcome measures across the world. To ensure that RPC can also contribute, we would suggest that these core outcome measures include instruments available in the majority of RPC. This, for example, could mean the use of radiographs rather than magnetic resonance imaging (MRI) as standard outcome measures. Or it could mean the more rapid development of ultrasound techniques (which are more resource-efficient than MRI) as outcome measures. This would ensure that valid comparisons can be done when studies are carried out both in resource-rich and resource-poor countries.

COST

It is also appropriate to consider ways to make expensive biologic agents more accessible to the large populations of patients in RPC. There may be ways to help decrease the costs of these drugs in RPC. As with several other expensive drugs in the developing world, these biologic agents could be sold at a discounted rate in countries defined by the World Bank as poor. (This is not meant to imply that the drug should be sold at a loss, merely at a significantly lower margin.) With anti-tumor necrosis factor (TNF) therapies, for example, it may be possible to package the TNF blocking agents in dosing units that increase the likelihood that vials of infliximab are fully utilized. Also, anti-TNF responders may be able to remain well controlled with less frequent dosing after an initial induction period with intensive therapy, allowing increased intervals between anti-TNF administration. Research in this area may allow more efficient use of anti-TNF drugs worldwide and such research can be encouraged in RPC.

Biologics may induce remission in various inflammatory rheumatic diseases, thereafter allowing maintenance with less expensive medications. Similarly, direct, careful, head-to-head trials of combination DMARD versus expensive biologics may lead to alternative, less expensive, strategies to treat rheumatic diseases. Again, research into the feasibility of such an approach is appropriate.

Even in Western countries, infrastructure costs, such as nursing and other support costs, are often underestimated. These costs are necessary to ensure the safe and effective administration of these biologic agents. It is essential that RPC ensure such support is available when using these therapies, particularly in the context of the need to fund local public health priorities such as malaria and HIV.

PHARMACOLOGY

Given the expense of producing proteins such as adalimumab, etanercept, and infliximab and given the advances in understanding of inflammatory and immunological processes, it is likely that xenobiotics (small molecules, including oral medications) will be found to replace the subcutaneous and intravenous biologics of today. Until then, use of biologics outside their presently indicated uses can be encouraged in rational, scientific ways, such as systematized anecdotal studies and case series and various forms of cohort and controlled trials. In fact, these studies need not be limited to countries with well-established research infrastructures but can also be done in countries that are striving to establish such research, including parts of Africa, South America, the Pacific Rim, and Asia.

CONCLUSION

We welcome the era of biologics as therapeutic agents in the rheumatic diseases, with their promise of clinical remission and prevention of structural and visceral damage. We consider it important, however, to draw the special needs of the resource poor countries (and attendant opportunities) to the attention of industry and the international rheumatology community.

Our desire is that all patients with inflammatory rheumatic diseases, regardless of where they live in the world, will be treated to at least a minimum standard of evidence based care.

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