

IMMUNOMODULATION IN THE CRITICALLY ILL

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SOURCE

N. R. Webster and H. F. Galley (2009) *Immunomodulation in the critically ill*. British Journal of Anaesthesia. 103 (1):70–81. doi:10.1093/bja/aep128

INTRODUCTION

The immune response is an essential network of cells, tissues, and organs that work together to provide a defence mechanism for the host organism. The primary targets of the immune system are microbes, parasites, and fungi that can cause infections. However, the system may become defective, disorganized or overactive, reacting to host tissues and causing disorders such as arthritis, allergic reactions and implicated in other conditions such as diabetes mellitus[16] among others, probably due to the recently identified Th 17. With such vital role, a mechanism of modulating the action of the system is essential.

The immune system is composed of two arms that work closely together, the innate immune system being more active early in an immune response while the adaptive immunity becomes progressively dominant over time.

Current medications used to modulate the immune system mainly exploit the mechanism of action of the immune system, blocking or enhancing some essential steps in the immune response cascade to provide their actions.

In the critically ill patient, the role of the immune system becomes even more evident as various conditions may come into play simultaneously, hence the essence of the current study.

During the review of the article, '*Immunomodulation in the critically ill*' a publication of the **British Journal of Anaesthesia**, the reviewer will provide a summary of the article, then analyse the structure followed by a critique of the work. This will be followed by an analysis of the objectivity and stability of the article. The review will also analyse the tables presented in the article. Recent advances related to the topic will also be examined followed by a conclusion of the article review.

REVIEW OF LITERATURE

Immunity indicates protection from a disease, and this state is afforded by the immune system whose function is to detect and eliminate foreign substances that may cause tissue injury or disease.

Being such a vital system, the immune system has received an overwhelming interest from researchers in a bid to find new immunomodulatory medications. As a consequence, literatures abound in this topic with the results as varying as the authors. Some of this literature will be reviewed below.

Goodman & Gilman^[5] classified the immunomodulators as immunosuppressants, tolerogens and immunostimulants. Their immunosuppressants included glucocorticoids, calcineurin inhibitors, antiproliferative agents and biologics (antibiotics). They noticed the importance of these drugs but noted their dark sides which involves life-long treatment and nonspecific immune system suppression thus exposing the patient to higher risk of cancer and infection

They also found a handful of immunostimulants to be used in clinical practice, among which were levamisole, recombinant cytokines, Bacillus Calmette Guerin and the notorious thalidomide, which despite its unenviable legacy of birth defects when administered to pregnant women, is said to still be indicated in the treatment of multiple myeloma and *erythema nodosum leprosum*, although in a very well controlled environment.

To minimize the side effects of both the immunostimulants and the immunosuppressants therefore, Goodman and Gilman proposed more studies on the tolerogens which if successful, would represent a true cure for many conditions.

Dermot Gleeson, Michael A. Heneghan^[7], while writing the guidelines of the management of autoimmune hepatitis, focused their attention in the management of autoimmune hepatitis where they stated that major strides had been made in the 1970s and 1980s in the management of this condition but that in recent years, there has been an acute insufficiency in clinical studies in the condition which has led to many unresolved questions in the subject matter.

On a brighter note, while writing in the *Journal of Clinical and Experimental Immunology*, Jolles et al^[2], lauded the recent advances in the understanding of the mechanism of action of and expansion in the use of intravenous immunoglobulins while noting that their major drawback was the cost of preparation and the logistical problems associated with their administration.

ARTICLE SUMMARY

The article *Immunomodulation in the critically ill* was aimed at elucidating the intricate cascade of activities resulting to immune response while providing critical insights into the role of immunomodulators in the management of conditions in the intensive care unit and their use in

the critically ill. It was also aimed at evaluating the different clinical studies that have been carried out in a bid to find new immunomodulators.

To attain these objectives, the researchers presented an overview of the functioning of the immune system, highlighting its regulation while making an inventory of the different disease conditions that are common in the critically ill patients that necessitate the use of immunomodulators together with possible management strategies as well as the different studies that have been and are currently being conducted to find new drugs to manage the given conditions.

The main findings of this study were that immunomodulation had both beneficial and undesirable effects with the level of immunomodulation apparently important—high dose vs low dose, short duration vs long duration; and the timing were also found to be seemingly crucial. The researchers also concluded that many of the studies to find new immunomodulators may have proved to be futile because the stage in the inflammatory process of the patients recruited for the studies were unknown.

The recommendation was therefore the necessity of evaluating the stage in the inflammatory process that the patient is at and then tailoring the appropriate therapy to the individual patient.

ARTICLE STRUCTURE

Immunology is one of the most difficult to understand aspects of biology for a novice, therefore the structure of an article on the subject can either attract or deter potential readers, an aspect that Webster et al seem to understand perfectly well.

In writing the article, Webster and colleagues started with an abstract that presented a very perfect summary of the article.

They continued presenting the article in a chronological manner with a background to the subject, providing an essential insight into the immune system and the basics of its function.

Following the background was an exploration of the various medications that have immunomodulatory potential that are used in the clinical setting.

This was trailed by an emphasis on the use of immunomodulators in the management of sepsis and acute respiratory distress syndrome, conditions common in the critically ill and in whose management are implicated immunomodulators.

Subsequently, the researchers presented a review of the different approaches that have been exploited in the not too distant past and some that are still being studied in a bid to discover new immunomodulators and explored the possible reasons why most of these studies have failed and provided a way forward into future studies on the subject.

The researchers concluded the article with a statement on the source of funds for the study.

The fact that the article was presented in short paragraphs that concentrate on a particular aspect of the subject makes reading very feasible. Summarizing, the article was well structured to enable easy understanding of a very complete content, even for a novice.

ARTICLE CRITIQUE

AUTHORITY

The authority of the article can be assessed from the following perspectives.

The authors: having been written by two academics in the academic Unit of Intensive Care and Anaesthesia of the University of Aberdeen and who have co-authored many other articles gives this article an enviable authority.

The Journal: the article's publication in the British Journal of Anaesthesia, the oldest and largest independent journal of anaesthesia, which reviews article to ensure they have the highest standards make the work a credible and authoritative source of information.

Funding: with funding from reputable sources as the Medical Research Council (a UK government agency), the Intensive Care Society (UK promoter of intensive care and critical care medicine) and the British Journal of Anaesthesia lends a lot of authority to the article.

With the above mentioned, it can be satisfactorily concluded that the article can be considered an authority in the subject matter.

ACCURACY

The article *Immunomodulators in the critically ill* can be said to present a very accurate piece of research. This statement can be supported from the fact that most of the literature referenced in the write-up supported the findings of the researchers. They all had a common consensus in the fact that the works cited also appreciated the role of the immunomodulators in managing conditions associated with the critically ill patient.

They may have been some variations in the interpretation of their findings but most of the articles shed light on the fact that studies to find new immunomodulators have failed due to various reasons and there is a need of a radically new approach in research in this field of science.

With this background, the article can be said to be accurate with respect to its references.

CURRENCY

In writing this article, the authors made reference to eighty five publications dating as far back as

1976 to publications as recent as 2008. Also the article makes reference to very recent discoveries in the field of such as the recent study on the toll-like receptor 4. These make the article very comprehensive and informative. With such recent referencing coupled with the fact that the article was actually published on May 27, 2008 after review makes the article a very recent publication. The discussion reflects current thinking about these conditions.

RELEVANCE

With more and more patients being admitted in the intensive care units than in the past, and with the recent shedding of light on the role of the immune system in the management of some very severe conditions implicating the immune system, there is general interest in articles of this sort, hence its relevance.

However, the very comprehensive nature of the subject matter undermines the article's relevance to the general public as they will find it very difficult to understand. The article is nonetheless very relevant to the scientific world and especially to those involved in academic and medical research.

With respect to the content, I think it very much reflects the title of the article; hence the content is very relevant to the title.

OBJECTIVITY

The information provided by the article was well developed without any sign of bias on the part of the authors. The literature matched with the author's findings in most of the cases.

The data presented were not only objective and informative but were very well tailored for the understanding of a novice in the field.

The objectivity of the article was further supported by the fact that the findings and conclusions of the authors were in line with the recent and contemporary thinking in the subject matter.

STABILITY

Having been carried out in an academic setting by highly qualified academics and having been published in a journal with such a reputation, the article is stable as a source of information.

ANALYSIS OF TABLES AND FIGURES

The article had four tables and three figures

Figure 1 showed the intracellular signalling pathways and how external inflammatory stimuli induce cytokine synthesis. Figure 2 was a superimposition on Figure 1 of the various sites at which immunotherapy can be altered by modification of the signalling pathway.

Figure 3 indicated the various phases of sepsis and sought to explain anomalies that are associated with immune response.

Table 1 detailed some recent and ongoing trials of immunotherapy at the time while table 2 presented the immune effects of opioids with table 3 reviewing the definitions of sepsis and shock according to the American Thoracic Society and the American Society of Critical Care Medicine while table 4 presented the problems and challenges of immunotherapy in human sepsis

In all, the figures were quite informative to the reader and the tables, straight forward, providing some essential insight into the subject matter to an informed reader.

RECENT ADVANCES RELATED TO THE TOPIC

SOURCE

U.S. Patil, A.V. Jaydeokar, D.D. Bandawane. Immunomodulators: A pharmacological review. *International Journal of Pharmacy and Pharmaceutical Sciences*, vol 4, suppl 1, 2012

In a related article, Immunomodulators: A pharmacological Review, published in the *International Journal of Pharmacy and Pharmaceutical sciences* on November 13, 2012, Patil et al sought to make an inventory of all immunomodulators, natural or synthetic, providing a basis of their mechanism of action as well as their classification, therapeutic uses and side effects.

To achieve this goal, Patil et al went about reviewing all the relevant literature about the contemporary immunomodulators while at the same time reviewing studies of new plants and chemicals with potential immunologic properties.

As part of their findings, they noted the improvements that have been made in recognizing the contributions of natural herbs in the advances of immunomodulation.

Noticeable, was the revelation of recent studies carried out in Russia on some Siberian plant extracts. These studies proved *Cirsium setosum*, *Aconitum baikalense*, and *Saussurea controversa* as potent natural immunomodulators. The extract of these plants, though dissimilar chemically, had shown similar effects on the immune system and have been successfully used in the treatment of benign and malignant tumours, anti-biotic resistant infections, polyarthrititis and psoriasis among others which conventional medicines find difficult to manage.

Even though their article came three years after that of Webster et al, Patil et al had similar lines of thought on the fact that immunomodulation is an aspect of science that is still very much uncovered and complicated and on which much research is still needed to shed light on some of its enigmas.

They also similarly concluded that the immunomodulators are becoming a viable adjunct to

conventional treatment protocols and stand a huge chance of becoming the treatment of choice of many disease conditions in the 21st century.

CONCLUSION

The immune system has evolved to protect the host from invading pathogens and to eliminate disease. Protection from infection and disease is provided by the collaboration of the innate and adaptive immune systems. At its best, the immune system is intricately responsive to invading pathogens while retaining the capacity to recognize self-antigens to which it is tolerant.

In the critically ill, this role becomes even more important as these patients are more in need of a responsive, yet tolerant immune system.

Webster and Galley, in their article '*Immunomodulation in the critically ill*' presents an objective evaluation of the state of knowledge in the field of immunomodulators and presents the findings of studies designed to find new immunomodulating drugs.

The study findings reveal the importance immunomodulation in the critically ill patient while stressing the need importance of closely evaluating the state of any client for immunomodulation and the need to tailor medications to the specific need of such patients.

It also presents the common fate that most studies designed to find new drugs with immunomodulatory potential have suffered. In an attempt to provide answers to the puzzles of the studies described, the article recommends, among other things, the need for closer monitoring of patients and the use of more than one agent at any time. Also, well-designed studies using a more focused patient group were required.

Upon implementation of these recommendations, new arenas for discovery of immunomodulatory agents may be exploited while elucidating other properties of these agents as the diagnostic capacity of soluble Toll-like receptors (sTLR)[17], among other uses.

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