Dear Doctor,

Season’s Greetings!

Maintaining immune competence throughout the life is one of the keys to long-term sound health & optimum productivity in animals.

However, when animals are under stress of production and reproduction or infectious agents, their natural immune system gets engaged in fighting off those challenges. In an on-going fight, the cows immune system can itself begin to weaken. Besides good nutrition for maintaining a healthy immune system; a variety of chemical and biological substances have been used in an attempt to non-specifically stimulate the immune system in several chronic diseases and suspected conditions of immunodeficiency. In great majority of the cases, such use has been entirely empirical with varied degrees of success. Levamisole has perhaps received the most attention since its first demonstration in 1971 that showed immune enhancing properties in brucella infected mice.

In this issue we discuss the significance of immunomodulation therapy in dairy animals. Hope you find it interesting.

Happy Reading!!!

Dr Arun Atrey
President & Head,
Global Animal Health Business
Cadila Healthcare Ltd.
Introducing Immunomodulation Therapy in Dairy Animals

Introduction
Animals live in an environment inhabited by infectious agents with the ability to attack their bodies and cause damages to different organs or end their lives. To protect themselves from such invasion, they have a system of immunity that identifies and eliminates millions of different pathogens or other harmful agents and minimizes the damages. The immune system is a dynamic and complex system whose purpose is to protect bodily functions and to get rid of harmful organisms. Cells in this system form physical barriers that prevent entry of pathogens, can secrete molecules with antimicrobial actions, and secrete signalling molecules that help to activate, direct and stimulate the immune response.

Lack of immunity is the cause of many diseases. Lymph node plays an important role in maintenance of immunity. There are many researches going on development of vaccines to prevent immunosuppression for particular diseases, but they are specific. Vaccine formulations often require adjuvants for increased immunological efficiency and better vaccination schedules. It has been observed that many plants are used for nonspecific activation of immune system. A number of plants used in traditional medicines for rejuvenation therapy and chronic ailments have been shown to stimulate immune responses and several active substances have been isolated. But it has been observed that the active content in plants vary from place to place and seasonal variation with a huge controversy of heavy metal contents. Even the immuno-stimulant effect can be due to some synergism. The use of medicinal plants in modern medicine suffers from the fact that though hundreds of plants are used in the world to prevent or to cure diseases, scientific evidence in terms of modern medicine is lacking in most cases.

The Immune System:
The immune system is a complex group of cells, tissues and signalling molecules that work together to protect the body against foreign substances. The body’s largest immune organ is the lymphoid tissue, which spans the entire intestine. The intestinal mucosal epithelium is the first line of defence, acting both as a barrier and as a source of secretory immunoglobulin IgA. This tissue is susceptible to damage and degraded immune function, particularly during times of stress, such as dietary change, high production level and age related changes in the immune system itself. The immune system comprises of innate (non-specific) and acquired (specific) immunity. Natural Killer (NK) cell, complement system, macrophages, antigen presenting cells (APCs) and neutrophils make up the innate immune system. The acquired immune response, comprises of humoral and cell mediated components. In addition, the immune system is an active participant in autoimmune disease, hypersensitivity reaction and transplant tissue rejection.

The innate immune system has been defined as consisting of those functions that are nonspecific in nature and with which the host is born. Innate immunity provides the first line of defence against invading pathogens. However, some pathogens have developed the ability to escape detection or clearance by the innate immune system. Additionally, parturition, lactation and diet influence the effectiveness of the immune system. Better understanding of the immune system has the promise of being able to augment or direct its action when the ability of the immune system to clear an infection is compromised or insufficient.

Two Major Branches of the Immune System

Acquired Immunity
This is what most producers think about for their herd-things like vaccines and antibodies

Innate Immunity
This is the first cellular defense against bacterial invasion, where macrophages and neutrophils respond to quickly kill bacteria

Immune Suppression:
Immune suppression literally means diminished immune responsiveness. Immune system is a highly diverse part of our bodies that fights disease. It involves cellular and non-cellular mechanisms that are often interdependent. Stress, nutrition, physical & physiological status, disease conditions and prolong medication etc. may result in immunosuppression in animals. Periparturient immunosuppression is very common in dairy cows. Endocrine changes and physiological stress during transition lead to dysfunctional immune response.

Immunity is a whole body system that protects animals from infection:

Ref.: Tizard IR. Veterinary Immunology. 9th ed. St Louis, MO: Elsevier Inc; 2013:1-10, 30-51.
Levamisole has influenced host defence by modulating cell-mediated immune response, humoral immunity response and enhancement of macrophage and polymorphonuclear cell function. Levamisole modulates immune function at 2 to 3 mg/kg body weight. Several researches have been performed to evaluate these immunomodulatory effects of levamisole for prevention and treatment of different diseases, but results of these studies have been inconsistent. Various scientific reports on Levamisole showed the beneficial effect in enhancing immunity status of animals as well as controlling incidences of different diseases or stressful conditions. However, the timing, dose of administration and extent of stress appears to be a limiting factor of immunomodulation activity of Levamisole in many cases.

Levamisole as an Immunomodulator:

Levamisole is one of the ideal contenders to help in modifying immune response because of its immunomodulatory effect. Levamisole is mainly used as anthelmintic agent in veterinary purpose. But in some countries its use is limited to immunomodulatory agent in domestic animals and humans. It is known that levamisole stimulates cell-mediated immune reactivity by potentiating the rate of T-lymphocyte differentiation, the sensitivity to antigens and mitogens and activity of phagocytes. Administration of a single dose (2.5 mg/kg) of levamisole results in immunomodulatory effect for about 48 hours. Intermittent treatment with one third of the anthelmintic dose (2.5 mg/kg) results in more effective immune response. (Metin Pancarci et al. Katkas niv Vet Fak Derg 15 (1): 25-33, 2009)

In a study to evaluate the effect of immunomodulatory drugs in uterine microbial load in repeat breeding cows and the conception rate; levamisole (@2.5 mg/kg for 3 weeks) was found to be most effective for establishing higher conception rate in comparison to other mode of therapies. It was observed that cows receiving levamisole, recorded a highly significant rise of total IG after the treatment. Similarly, a highly significant decrease in bacterial load was observed. The overall conception rate in this group was 60% at first and second insemination. (P K Swain et al. Indian Journal of Animal Reproduction 32 (2) : Dec 2011)

Levamisole treatment showed faster involution of the cervix uteri in cows with normal vaginal discharges as oppose to those with pathological discharges. This result implies that immunomodulatory treatment could be more effective in healthy cows for involution of the cervix uteri. Similarly, shorter period for uterine involution has been reported in cows treated with levamisole during dry period. (Metin Pancarci et al. Katkas niv Vet Fak Derg 15 (1): 25-33, 2009)

94 Holstein cows at dry period of a dairy herd were selected randomly. Levamisole was administrated orally to 46 cows (test group) at a dose of 2.5 mg/kg at 3 days interval, during the first 45 days of dry period. Forty-eight cows were chosen as control group. All cows received a dry cow mastitis ointment at drying off. The treatment was ceased approximately 2 weeks before expected time of parturition. Each cow received 16 treatments on average. Results showed that the incidence...
of new mastitis cases were significantly different between the test and control groups (29.3% vs. 45.8%, respectively). Though positive response to treatment of existing intra-mammary infections was not significantly different between the two groups, the results of this study showed that levamisole exerts its effects through prevention of new mastitis cases. (N. Farzaneh et. al. School of Veterinary Medicine, Ferdowsi University of Mashhad, Iran)

- Studies have shown beneficial effects of levamisole (2.5 mg/ kg b wt for 6 wk) in decreasing mastitis and fetal mortality in dairy cows. (Flesh et al. (1982), Vet. Rec. 111: 56.)

- In a study of transported feeder calves, reduced mortality was found in calves that were treated with levamisole upon arrival at the feedlot (6.8%) compared with calves injected with levamisole at an order-buyer barn prior to transport to the feedlot (9.0%) or with control calves that did not receive levamisole (13.6%). (Brazle et al., J. Anim. Sci. 59:3822, 1984).

- Levamisole given 7 days before, and again together with vaccination, in eight pregnant buffaloes showed enhanced antibody response to FMD virus in serum. (Z. I. Qureshi et al.: Vet. arhiv 70 (2), 59-66, 2000)

- The study was conducted on 48 cross breed cattle which were identified as clinical cases suffering from cutaneous papillomatosis (warts). Lesions were found as clusters especially on the shoulders, head, neck, udder, teats, dewlap, and eyes and in the ear canal. The ailing cattle were given Levamisole @ 2.5 mg/kg body weight orally for six days as per the schedule (1st, 3rd, 5th, 7th, 9th and 16th day). Complete healing was observed 10—15 days after the last dose of administration. In case of extensive lesions, two more doses at an interval of 10 days yielded good results. ( P Kumar C et. al. Research & Reviews: Journal Of Veterinary Science and Technology Vol 3, No 3 (2014)

<table>
<thead>
<tr>
<th>Suggested Dose Schedule of Levamisole:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>To control post-partum complications like retained placenta, metritis, pyometra, foetal death in dairy cows</td>
</tr>
<tr>
<td>To increase conception rate in repeat breeding</td>
</tr>
<tr>
<td>Prevention of Mastitis (Treatment of subclinical mastitis)</td>
</tr>
<tr>
<td>To enhance immunity along with vaccination</td>
</tr>
</tbody>
</table>

**Conclusion:**

Levamisole influences host defence by modulating cell-mediated immune response, humoral immunity response and enhancement of macrophage and polymorphonuclear cell function. Levamisole modulates immune function at 2 to 3 mg/kg body weight. Several researches have been performed to evaluate these immunomodulatory effects of levamisole for prevention and treatment of bovine mastitis, but results of these studies have been inconsistent. Levamisole restores depressed immune responses in animals & humans but has little or no effect in immunologically competent individuals, as its effects are related to improve deficient activities of macrophages & T-lymphocytes. To achieve better clinical effects, it is advocated to use as an adjunct therapy, along with some other primary treatment. Various scientific reports on Levamisole showed the beneficial effect in enhancing immunity status of animals as well as controlling incidences of different diseases or stressful conditions. However, the timing, dose of administration and extent of stress appears to be a limiting factor of immunomodulation activity of Levamisole in many cases.