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Signs, symptoms and complications of non-Hodgkin's lymphoma according to grade and stage in south Iran

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Extended Abstract

Background: Non-Hodgkin's lymphoma (NHL) is a heterogeneous type of neoplasm of the lymphatic system. In order to have a more accurate and early diagnosis we need to be familiar with signs, symptoms and complications of lymphoma in early stages besides pathology and immunohistochemistry. Materials & Methods: This prospective study included 110 cases of NHL that were followed since February 2012 till November 2013. Biopsies were taken from all the patients besides bone marrow study. Signs and symptoms were categorized into "B" symptoms, general, lymphadenopathy and extranodal involvement, and we compared the frequencies by stage and grade and immunohistochemistry types. Descriptive analysis determined the mean, median, standard deviation and frequency of the variables. Chi square test was done to compare the frequencies of signs, symptoms and complications by stage, grade, sex and age of the patients. The significance level was determined 0.05 in these analyses. Means of quantitative variables were compared in different levels of qualitative by one way ANOVA test. Independent sample t-test was also used for this analysis Results: Between the 110 cases, 88.9% had B-cell and 11.1% T-cell type NHL with mean age 48.5±18.6 years. "B" symptoms and lymphadenopathy were more common in men. Cervical lymphadenopathy was the most common sign (44.8%). Hematologic, bone marrow, bone and neurologic lesions were the most common complications. All complications were more common in males. "B" symptoms were seen mostly in stage III, general signs and symptoms in stage IV, and lymphadenopathy in stage II. Intermediate grade was the most common grade in relation to all the signs and symptoms. In this study 12 (10.9%) patients had relapse, with neurologic and bone marrow as the most common sites of tumor recurrence. Conclusions: There is a meaningful relationship between male gender for NHL and anemia that can be due to higher incidence of bone marrow involvement and stage IV disease in male cases. We also found a strong relationship between low grade NHL and age. The prevalence of NHL was higher in male patients however it was reverse with a significant difference in patients who had high serum ESR level at presentation which can suggest etiologic differences and the role of immunologic factors in evolution of this malignant disease. Extranodal involvement was also more common in female group.

Keywords: Non-Hodgkin's lymphoma; Immunohistochemistry; Lymphadenopathy; NHL; Anemia;

Biography

Haddadi S, MD, is an International Medical Graduate from Iran. She graduated and was licensed from Shiraz University of Medical Sciences in 2014, then practiced as a primary care physician in rural and underserved areas in South of Iran in Khafr clinic for 17 months. She has been attending Kaplan Medical Test Preparatory in Chicago since Sept 2015 to sit for the USMLE exams and apply for Internal Medicine Residency in the US. During her internship in Shiraz, she worked at inpatient and outpatient clinics, as well as the oncology hospital wards. While providing care for cancer patients, she investigated and studied the signs, symptoms and complications of 110 patients with Non-Hodgkin’s lymphoma (NHL), at presentation and relapse, and defended her thesis about NHL with the score of 19.83/20 by graduation from Shiraz University.

Transformation of inpatient care - It is time to revolutionize primary care

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Extended Abstract

The healthcare landscape is constantly evolving whether it is influenced by legislative reform, latest technology or new drugs and treatment protocols. What continues to remain consistent though is escalating costs and poor patient outcomes, regardless of our ability to integrate the best in evidence-based medicine into our practice. Patients who cannot afford insurance make regular use of ER, this is a poor use of highly trained staff and scarce resources, it also does very little to provide effective management of chronic diseases. The relationship between primary care physicians (PCP) and acute care can be tenuous and is hindered by ineffective communication, often PCP not being notified when a patient came to the hospital. Improving the relationship between PCP and hospital is vital if we improve health of patients and health system as a whole. The role of hospitalists is not one that is intended to replace primary health care services; rather it is a part of patientâ larger health care team. Hospitalists work towards improving transitions in care and seeing that treatment received in hospital is appropriately coordinated with PCP at discharge. There is a lot of misunderstanding about hospitalists. Increasing number of hospitalists in the United States is reflection in the ever increasing specialization in medicine that sees patient care fragmented into a collection of body parts. Specialists too focused on their organ system issues and quickly move onto the next patient in a stream of referrals from the community and within the hospital. On the other hand, hospitalists offer more comprehensive care that addresses immediate and chronic health issues that shown to reduce length of stay and the number of hospital acquired infections. Hospitalists are also on the front line of quality improvement initiatives and are able to initiate and drive quality metrics that improve care and reduce costs. Another advantage of hospitalists is to understand business component of medicine while maintaining a patient-centered focus. This is of benefit to both patients and hospitals, as hospitalists see a significant number of patients in diverse clinical settings, they are uniquely positioned to understand the larger issues facing the hospital, rather than just those within a specific unit or speciality area. Hospitalists not only improve the inpatient experience, but they also set patients up for the best transition. Rather than suggesting that hospitalists are the embodiment of everything that is wrong with the current state of our healthcare system, hospitalists should be thought of as effective and efficient care coordinators to view patients holistically. Improving patient outcomes is not only the end; rather it is the responsibility of all care providers to put their patientâ front and center in both the hospital and in primary care. Hospitalists set patients up for a successful transition back into the community and more effort in building stronger relationships with primary care teams. Ultimately, quality care provision to patients should serve as a prime motivating factor regardless of location.

Keywords: Primary care physicians; ER-Endoplasmic Reticulum; Acquired Infections; Quality Matrix.

Biography

Venkataraman Palabindala held various leadership positions starting from residency as Chief Medical resident at GBMC hospital, Clerkship director and Home health director at SAMC hospital, founder and president of Alabama Wiregrass Chapter of SHM. He is now Division Chief of Hospital Medicine at University of Mississippi Medical Center (UMC) and Chapter Leader for Gulf States SHM chapter. He also contributes to other roles at UMC as Medicine Dept Physician Advisor, Denial steering committee lead, Length of stay task force lead. He received both Fellow of American College of Physicians and Senior Fellow of Hospital Medicine degrees within 4 years after his graduation and listed as youngest hospitalist in ACP top 10 for year 2016. He have been part of SHM National Leadership committee, SHM National IT committee, and won Silver chapter award as Wiregrass chapter leader. he have been part of 30 posters in different state and national meetings. He won resident research award all 3 yrs during residency. My primary interest is resident education, patient safety, health informatics.

Diagnosis and management of acute kidney injury in intensive care

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Extended Abstract

Acute kidney injury (AKI) is defined as rapid reduction in kidney functions resulting in failure to maintain fluid, electrolyte and acid-base homeostasis. AKI is reported to occur in 15-20% of all ICU patients and approximately 5% of them may require dialysis during ICU stay. Typically patients with AKI develop oliguria or anuria and may present signs and symptoms of fluid overload. Oliguria is defined as if urine output <1 ml/kg/hour in infants, and <0.5 ml/kg/hour in children and adults for consecutive 6 hours; while, anuria is defined as urine output <50 ml/24 hours in adult patients. Broadly speaking AKI is classified into pre-renal, renal and post-renal depending upon the initial insult leading to AKI. Among them pre-renal is the most common cause of AKI, approximately 55-90% in the ICU setting. Renal causes like acute vasculitis, interstitial nephritis, contrast nephropathy, severe rhabdomyolysis are also contributing to a small proportion of these patients. Post-renal causes accounts for less than 5% of all others. The main stay of management of AKI depends upon early recognition and early diagnosis of renal insults. To diagnose AKI, these is wide range of investigations, but recently some new biomarkers have been identified which help to identify early onset of AKI. Among these biomarkers, neutrophil gelatinase associated lipocalin (NGAL) has been identified in early diagnosis of AKI due to cardiopulmonary bypass, contrast induced nephropathy, AKI due to sepsis, early recognition of AKI after renal transplant. Some other biomarkers also have been identified for diagnosis of early AKI like, IL 18, KIM 1, Cystacin C and L-FABP. The initial management step of AKI is to treat the offending factors leading to renal impairment, e.g., treating dehydration and sepsis, stopping offending drugs like NSAIDS, aminoglycosides & ACE inhibitors, well rehydration before and after intravenous contrast agents to prevent contrast induced nephropathy. A quite fair number of patients end up requiring dialysis and continuous renal replacement therapy (CRRT) is the most effective method for dialysis in these patients. It may improve survival rate by 30%. There is large debate about early vs. late start of CRRT. But, all depends upon the clinical judgment and other associated parameters to make decision to start early CRRT in these patients. About 10% of all AKI patients may require chronic dialysis and further follow up. So, AKI is one of the serious problems in intensive care, its early recognition and management has a vital role in the management of critically ill patients

Keyword : Streptomyces griseocarneus; Antitumor; Hydrated Magnesium Sulphate; Potassium dihydrogen Phosphate; Dipotassium Hydrogen Phosphate; Bacterial resistance; Antimicrobial activity; Fermentation; Sensitivity;

Biography

Khalil Ahmad has completed his MBBS from Punjab Medical College Faisalabad, Pakistan in 1998. He then moved to FPGMI Shaikh Zayed Hospital Lahore, Pakistan for Residency Program in Internal Medicine. He has passed Fellowship Exam in Internal Medicine (FCPS) from College of Physicians & Surgeons in 2005 and moved to Dubai, UAE in 2006 and joined Rashid Hospital, Dubai Health Authority and also qualified Membership Exam from Royal Colleges of Physicians, UK (MRCP) in 2011. He has completed European Diploma in Intensive Care Medicine (EDIC) conducted by European Society of Intensive Care Medicine in 2013.

Critical Importance of New Generation Government Engagement Navigating Government Healthcare Reforms and their impact in USA, Europe, Turkey & Emerging Markets

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Abstract

Pharmaceutical, Biotech and Medical Device companies are constantly evaluating how decisions at the US, Europe, Turkey and emerging markets are taken at the federal and state level and how it will impact provider and patient access and coverage to their therapies.

To gain these critical insights, Government Affairs & Medical affairs teams require speaking with those on the frontlines of healthcare delivery - physicians, allied healthcare professionals, payers, and patients. New generation government engagement and commercial diplomacy approach developed by ICG (Istanbul Consulting Group) will be provided with unique cases.

Dr. Yavuz Selim SILAY a global leader and seasoned expert in Government engagement, Commercial Diplomacy, Corporate Communications, Government affairs & Medical Affairs will discuss how companies utilizing Government Affairs and Medical affairs teams should engage decision makers, payers, physicians and acquire these insights in a convenient, cost-effective, and compliant manner in this current changing global regulatory landscape. Current Trends in Physician Entrepreneurship in USA Europe Turkey and Emrging Markets will be provided with unique cases.

Keywords: Immune necrotizing; Glutaryl coenzyme; Auto immune diseases; Electro myography; Intravenous immunoglobulin

Biography

Yavuz is the Co-Founder & CEO of MAIN (MaQasid Angel Investors Network) & chairman of Istanbul Consulting Group. MAIN is the fastest growing global ethical angel investor network investing in technology in Emerging Markets. ICG (Istanbul Consulting Group) was founded in 2013 and provided guidance to the Turkish ministry of health as part of a World Bank project. Yavuz is currently the Co-Founder of Bio Cube İstanbul Bio entrepreneurship & Innovation Center and Corporate Communication Director of Archem Diagnostics. He previously managed the largest distributor of Siemens Healthcare in Turkey managing 250 employees and director of Avcılar Hospital R&D Center. Previously he worked as the Market Access & Health Policy Director for AIFD in Turkey.

Yavuz previously worked as the Vice President of Ipsen pharmaceutical and Director of Teva pharmaceutical in USA managing large clinical trials as well as Investigator Initiated Trials and developing relationships with Key Opinion Leaders. Previously, Yavuz was the Associate Director at KV Pharmaceuticals and Director in Clinical

Development department at Forest Laboratories.

Yavuz earned his MD from the Faculty of Medicine, University of Ankara in Ankara, Turkey. He completed a clinical internship at Baylor College of Medicine in Houston, followed by continued research training at The University of Texas MD Anderson Cancer Center in Houston. He recently completed his Executive MBA at the Olin Business School at Washington University in St. Louis. Yavuz currently resides with his wife Dr. Kamile Sılay and their two daughters and one son in Ankara, Turkey.

Conclusion

Pharmaceutical, Biotech and Medical Device companies are constantly evaluating how innovation management can be improved and managing expectations of Key opinion leaders.

Current Trends in Physician Entrepreneurship in USA Europe Turkey & Emerging Markets

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Abstract

Pharmaceutical, Biotech and Medical Device companies are constantly evaluating how innovation management can be improved and managing expectations of Key opinion leaders.

To gain these critical insights for Physician Entrepreneurship, Our goal at Society of Physician Entrepreneur is to accelerate innovations in order to improve healthcare. We seek to empower doctors, other healthcare providers and entrepreneurs with the information, resources, connections, and experience they need to commercialize their ideas, inventions and discoveries. Current Trends in c in USA Europe Turkey and Emerging Markets will be provided with unique cases.

Dr. Yavuz Selim SILAY a global leader and seasoned expert in Physician Entrepreneurship, Government engagement, Commercial Diplomacy, Corporate Communications, Government affairs & Medical Affairs will discuss how Venture Capital and angel Investment networks are utilizing physician entrepreneurs to acquire these insights in a convenient, cost-effective, and compliant manner in this current changing global entrepreneurial landscape.

Keywords: Venture Capital; Physician Entrepreneurship; Global Entrepreneurial Landscape; Pharmaceutical; Biotech; Medical Device;

Biography

Yavuz is the Co-Founder & CEO of MAIN (MaQasid Angel Investors Network) & chairman of Istanbul Consulting Group. MAIN is the fastest growing global ethical angel investor network investing in technology in Emerging Markets. ICG (Istanbul Consulting Group) was founded in 2013 and provided guidance to the Turkish ministry of health as part of a World Bank project. Yavuz is currently the Co-Founder of Bio Cube İstanbul Bio entrepreneurship & Innovation Center and Corporate Communication Director of Archem Diagnostics. He previously managed the largest distributor of Siemens Healthcare in Turkey managing 250 employees and director of Avcılar Hospital R&D Center. Previously he worked as the Market Access & Health Policy Director for AIFD in Turkey.

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Conclusion

Pharmaceutical, Biotech and Medical Device companies are constantly evaluating how decisions at the US, Europe, Turkey and emerging markets are taken at the federal and state level and how it will impact provider and patient access and coverage to their therapies.

Fast disintegration tablets: Problems and Evaluation

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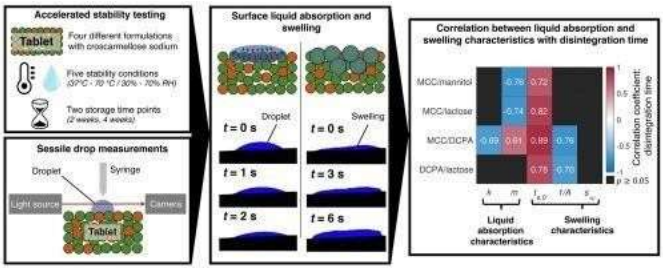
Abstract

Responding to the present demand of the fast Disintegration tablets, this study offers a trace-up analysis of the fast disintegration tablets to examine the ways of preparation and evaluation processes. It studies the short method to serve the patient who cannot swallow tablets for some reasons. The process of disintegration of pharmaceutical tablets is a crucial step in the oral delivery of a drug. Tablet disintegration does not only refer to the breakup of the inter-particle bonds, but also relates to the liquid absorption and swelling behavior of the tablet.

1- The study shows the use of the sessile drop method, analyzing the surface liquid absorption and swelling kinetics of four filler combinations (microcrystalline cellulose (MCC)/mannitol, MCC/lactose, MCC/dibasic calcium phosphate anhydrous (DCPA) and DCPA/lactose) with croscarmellose sodium as a disintegrant. Changes in the disintegration performance of these formulations were investigated and analyzed by quantifying the effect of compression pressure and storage condition on characteristic liquid absorption and swelling parameters.

2- The results indicate that the disintegration performance of the MCC/mannitol and MCC/lactose swelling characteristics affect the disintegration time, whereas DCPA/lactose tablets is primarily controlled by swelling characteristics of the various excipients. The analytic approach and discusse in this study enables a rapid (<1 min) assessment of characteristic properties that are related to tablet disintegration, to inform the design of the formulation, process settings and storage conditions



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Keywords: Streptomyces griseocarneus; Antitumor; Hydrated Magnesium Sulphate; Potassium dihydrogen Phosphate; Dipotassium Hydrogen Phosphate; Bacterial resistance; Antimicrobial activity; Fermentation; Sensitivity;

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Biography

Nawaf Ali Musleh Saleem is a Yemeni scholar and has completed his bachelor of Pharmacy from Kakatiya University, India, He has worked on Formulation and Evaluation of Canaglifozin Sustain Release Matrix Tablets. He has many experiences in the field of pharmaceutical medicine.

International Journal of Collaborative Research on Internal Medicine and Public Health 2022, Vol. 14, Issue 02, 001-002 Mini Review

In Renal Cell Carcinoma, the Role of Natural Supplement Compounds as Anticancer Agents

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Abstract

Renal Cell Carcinoma (RCC) is the most common kidney cancer that arises from the renal tubules, accounting for around 85% of all malignant kidney cancers. Every year, about 60,000 new instances of RCC are reported, with approximately 14,000 people dying from the disease. In the United States and other countries, the frequency of this has been steadily growing. A better understanding of RCC's molecular biology and genetics has revealed multiple signalling pathways implicated in cancer growth. Agents licenced by the Food and Drug Administration (FDA) that target these pathways have been reported to make significant advancements in the treatment of RCC. Because of their therapeutic value and enhanced survival in patients with metastatic disease, these medications have become the treatments of choice. Patients, on the other hand, eventually relapse and acquire resistance to these medications. The search for more effective medicines and preventative methods is necessary to enhance outcomes and find approaches for establishing long-term sustainable remission. One of these techniques to lessen the incidence of RCC is to treat it with natural products. Recent research has focused on these chemoprevention medicines as anti-cancer therapeutics due to their ability to limit tumour cell growth while avoiding the significant side effects associated with synthetic chemicals. The present state of knowledge on natural products and their mechanisms of action as anti-cancer medicines is discussed in this study. The information included in this study will be useful in determining whether these products can be used alone or in combination with chemotherapy to prevent and cure RCC.

Keywords: Carcinoma • Cancer cell • Immunosenesce • Natural supplement • Immunotherapy

Introduction

Renal Cell Carcinoma (RCC) is cancer that develops in the tubule lining of the kidney [1]. It is the most common type of kidney cancer in adults, accounting for nearly 85% of all malignant kidney cancers [2,3]. It can cause weight loss, fever, hypertension, hypercalcemia, night sweats, and malaise, among other symptoms. Despite its rarity, RCC is still one of the top 10 malignancies, affecting mostly those over the age of 45 [4]. Men are more likely than women to develop this malignancy, with the typical age of diagnosis being about 60 years [5,6]. Over the last two decades, its incidence rates have been steadily increasing by 2%-4% per year [7]. According to the most recent cancer data, almost 64,000 new instances of kidney cancer will be diagnosed in the United States in 2017, with around 14,400 persons dying from renal cancer-related complications [8]. Patients with this condition have a five-year survival rate of about 85 percent if they are diagnosed and treated early, but just 10% if they are diagnosed later [9]. With a better understanding of RCC's molecular biology and genetics, multiple signalling pathways linked to the disease's progression have been identified [10]. Agents approved by the FDA that target multiple pathways have resulted in significant breakthroughs in the treatment of RCC. Inhibitors of the mammalian target of rapamycin (mTOR) and tyrosine kinase inhibitors are two examples (TKIs). In patients with advanced RCC, these medications provided therapeutic benefits without lowering the overall quality of life and had a good influence on particular symptoms such as cough, fevers, shortness of breath, ability to enjoy life, and fear that the condition might worsen. Patients, on the other hand, eventually relapse and acquire resistance to these medications. Improved identification, prevention, and treatment strategies are needed to minimise the fatality rate linked with RCC. Natural items typically investigated in chemoprevention, i.e. the use of chemicals, bioactive plant compounds, or dietary components to block, inhibit, or reverse the formation of cancer in normal or preneoplastic tissue as therapeutics for the treatment of RCC, will be evaluated in this study. Many chemicals derived from natural products have been discovered to be effective as both preventative and therapeutic agents in previous investigations. They have been proven to improve the efficacy and tolerance of chemotherapeutic drugs in various tumours when used in combination with chemotherapy or alone. The present state of knowledge about the usefulness of naturally occurring anti-cancer drugs in the treatment of RCC will be discussed in this review paper. Epigallocatechin-3-gallate (EGCG), Englerin A, Quercetin, coumarins, curcumin, and other natural compounds have been studied for their impact on RCC.

Renal cell carcinoma and natural products

Natural products have been utilised for medical purposes for thousands of years, but researchers have only just begun to look into the function they play at the molecular level. These natural products are significant because their use in ancient history has been established and can be used in modern therapy with proven results. Indeed, natural goods have been employed as traditional medicines, cures, potions, and oils by nearly every major ancient civilisation, with many of these bioactive natural ingredients remaining unknown. Natural products have been utilised for therapeutic purposes since 2600 B.C. when oils from Cupressus sempervirens (cypress) and Commiphora species (myrrh) were documented as being used to heal ailments. Natural products have been pushed to the sidelines in recent medical history, with human-made medications generated from molecular biology and combinatorial chemistry practically always taking precedence. However, these medications are frequently prohibitively expensive. Furthermore, they frequently have terrible side effects that render them unsuitable for treating human ailments, such as having the opposite impact as planned. Herbal or natural remedies, in general, offer little to no adverse effects while generating excellent tumour therapy results. The therapeutic actions of the chemicals contained in these products, however, have not been well investigated in RCC. As a result, it's a good idea to look into the pathways that are influenced by the molecules found in these natural products. The fact that tumour cells frequently bypass the apoptotic process, allowing uncontrolled multiplication, is a key contrast between normal healthy cells and tumour cells. As a result, triggering apoptosis would be a viable therapy option. Tissue factor pathway inhibitor-2 (TFPI-2) expression is inversely associated with the aggressiveness of RCC cells. As a result, larger TFPI-2 concentrations would reduce the malignancy of these cells and, most likely, cause apoptosis. Green tea (Camellia sinensis) contains epigallocatechin-3-gallate (EGCG), which has anti-tumour activities in numerous malignancies, including RCC. It suppresses tumour development and invasiveness in RCC by upregulating TFPI-2 expression and inhibiting DNA methyltransferase (DNMT) activity. Multiple independent investigations have demonstrated that EGCG is a highly effective therapy in vitro. The data previously presented suggests a few ways to use EGCG. A large epidemiological investigation, for example, found an inverse relationship between green tea consumption and overall RCC tumour burden. Another option would be to combine EGCG with TKI or mTOR inhibitors to investigate if the combo sensitises tumour cells more effectively than either TKI or mTOR inhibitor alone. Sato et al. claim that EGCG administration increased the chemical sensitivity of vinblastine by inactivating Src and activating the c-Jun NH2-terminal kinase (JNK) de RCC cells via restoring the connexin 32 (Cx32) gene, a tumour suppressor.

Englerin A: Englerin A is a natural substance obtained from the root and stem bark of the African plant *Phyllanthus engleri*. Through a pharmacological screen of the NCI 60 (National Cancer Institute 60) cell line panel, it was discovered to preferentially inhibit the growth and viability of RCC cells. This natural substance is a guaiane sesquiterpene with a tricyclic structure that may be synthesised in a lab using a systematic technique. Multiple suggested mechanisms for Englerin A's suppression of RCC growth have been discussed in detail by Beutler and associates in a comprehensive review. Ramos' group has proposed that Englerin A can stop RCC cell lines from growing by causing necrotic cell death rather than apoptosis. In vivo studies have been few, and those that have been done on mice models suggest that the amounts of Englerin A required for anti-tumor efficacy are potentially deadly. If the results of this in vivo model properly reflect the effects of the natural chemical, it would be a significant barrier to its application in cancer treatment. The complex, on the other hand, is well worth examining. If a non-lethal derivative of Englerin A could be discovered and applied, it would be tremendously successful in treatment. Furthermore, the mechanisms by which Englerin A elicits anti-tumor properties are currently being debated. If it is discovered that Englerin A suppresses tumours through many mechanisms, it could be used to treat various cancers.

Quercetin: Quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavonoid pigment that can be found in a variety of foods, including tea, onions, grapes, and apples. Quercetin has been proven to have a chemopreventive effect in a variety of malignancies, including liver, lung, prostate, breast, and kidney cancers. When combined with other substances, this natural product has proven to be quite beneficial. When combined with hyperoside, quercetin exerts a therapeutic impact in 786-0 renal carcinoma cells. Downregulation of miRNA-27a is the mechanism behind this activity, which we haven't looked into yet in this article. Most natural compounds we've looked at use alternative mechanisms to cause apoptosis or necrosis. Meanwhile, a drop in specificity protein (SP) transcription factors is triggered by a decrease in miRNA-27a paired with an increase in ZBTB10 (the zinc finger and BTB domain-containing protein 10). These transcription factors are highly expressed in cancer cells, and quercetin's ability to reduce its expression demonstrates quercetin's therapeutic promise.

The chemopreventive action of EGCG was considerably reduced when it was methylated by the catechol-O-methyltransferase (COMT) enzyme in different malignancies. By reducing COMT activity, quercetin has been shown to boost the activity of EGCG in terms of bioavailability in animal models. Snail is a zinc-finger transcription factor that regulates EMT, migration, and metastasis in cells. In Caki-2 cell lines, silencing it with short hairpin RNA (shRNA) inhibited cell proliferation, cell cycle progression, cancer cell migration, and accelerated apoptosis. Quercetin, when combined with snail silencing, has much more potent suppressive effects on these cells. Quercetin has a lot of therapeutic potentials, which can be polished with more research and analysis. Sunitinib and isoquercetin, which is hydrolyzed in vivo to quercetin, are now being studied in conjunction. The researchers in this ongoing clinical trial believe that isoquercetin can minimise sunitinib-induced weariness, which is reported in 51-63 percent of advanced RCC patients.

Conclusion

Many agents, such as anti-angiogenesis and immunotherapy medicines, are currently available for the treatment of RCC (interleukin and interferon). Renal cell carcinoma is one of the deadliest malignancies, and late stages, despite the numerous therapy choices, are incurable. There is a definite need for drugs that are efficient against tumours while also avoiding undesirable drug reactions in the patient. Nature products have been presented as an alternative, however, few of these chemicals have been used on a broad scale in the treatment of cancer patients yet. Many natural chemicals have been demonstrated to be extremely successful *in vitro* and *in vivo* cancer models in recent studies, and history has shown that this class of drug has few to no negative side effects. EGCG, Englerin A, curcumin, resveratrol, quercetin, and honokiol are just a few of the natural substances that have shown promise in RCC preclinical trials. The anticancer mechanism of these drugs has been summarised. It's a good idea to keep looking into natural compounds as anti-tumour agents that don't have a lot of side effects, either alone or in a well-designed combination. Alpinumisoflavone is a plant isoflavon isolated from Erythrina lysistemon, and nothing is known about its anti-cancer properties in RCC. Wang et al. have discovered the mechanism of this natural compound's anti-cancer action, claiming that it inhibits tumour growth and metastasis through altering miR-101/RLIP76 signalling. A clerodane diterpene (CD) isolated from Polyalthia longifolia var. pendula leaves, 16-hydroxycleroda-3,13-dien-15,16-olide, has been found to suppress the proliferation of numerous human cancer cell lines. However, the mechanism of CD's anti-RCC activity is unknown. In RCC cells, a recent study revealed the mechanism of action of CD, suggesting that it inhibits cell growth and promotes mitochondrial-dependent apoptosis via the AKT, mTOR, and MEK/ERK pathways. According to a recent study, Korean red ginseng extract can boost sorafenib's anticancer efficacy by decreasing cyclic adenosine monophosphate response element-binding protein and c-Jun activation, inducing p53 phosphorylation, and improving sorafenib's chemosensitivity in RCC.

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Inflammatory Bowel Diseases and the Vitamin D Axis: Role, Current Uses, and Future Prospects

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Abstract

The idea that the vitamin D axis has immunoregulatory functions is gaining traction, with Vitamin D Receptor (VDR) status being the most important determinant of vitamin D's pleiotropic effects. Vitamin D stimulates the formation of antimicrobial peptides such as -defensins and cathelicidins, as well as autophagy and epithelial barrier integrity, as well as the shift toward Th2 immune responses. Vitamin D deficiency has been linked to a variety of chronic inflammatory disorders, including Inflammatory Bowel Disease (IBD). Inhibition of vitamin D pathways causes dysbiosis of the gut microbiome, which has been linked to the development of IBD in a molecular approach. The significance of the vitamin D axis in immune-mediated disorders is examined in this paper, with a focus on its interaction with the gut microbiome in the pathogenesis of IBD.

Keywords: Vitamin D receptor • Dysbiosis • Immune system

Introduction

Vitamin D is a steroid/thyroid superfamily pleiotropic hormone best recognised for calcium homeostasis, but it also has various non-calcemic actions, including immunological regulation, cell differentiation, and intercellular adhesion. After a two-step hydroxylation of the inactive precursor, cholecalciferol, the active form of the vitamin is formed. Cholecalciferol is hydroxylated at position 25 to produce calcifediol [25(OH)D3], an inactive intermediate that is then hydroxylated at position 1 to produce calcitriol [1,25(OH)2D3]. Vitamin D, both inactive and active forms, circulates through the bloodstream coupled to vitamin D-binding protein (VDBP). The active form has an effect through attaching to the vitamin D receptor, a transcription-regulating protein (VDR). Vitamin D deficiency has been linked to a number of immune-mediated disorders, as well as altered immunological responses to pathogens and an increased risk of infection and cancer [1-4]. Furthermore, its binding protein can directly mediate some immunoregulatory functions [5], and its receptor, which is also expressed on immune cells, is involved in inflammatory pathway modulation. Inflammatory Bowel Diseases (IBD) are chronic inflammatory illnesses that can affect the entire gastrointestinal system and are thought to be caused by inappropriate and persistent immune activation in genetically susceptible individuals in response to gut luminal chemicals [6-8]. Vitamin D insufficiency is widespread in Crohn's disease (CD) and ulcerative colitis (UC), the two most common forms of IBD [9,10]. In this context, we examined the current literature to highlight accumulating information about the crucial function of the vitamin D axis in the setting of IBD, with a focus on the interplay between the gut microbiome and Vitamin D/VDR-mediated genetic and immunological responses. Our findings suggest that a balanced intervention on VDR function, including both vitamin D analogues and probiotics, could be a complementary strategy to IBD treatment.

Why is the vitamin d axis being targeted in IBD?

The vitamin D axis is made up of vitamin D, its binding protein, and its receptor, and it has a lot of intriguing qualities in terms of gastrointestinal physiology. Vitamin D's physiological activities are mediated by the VDR, a nuclear receptor superfamily ligand-dependent transcriptional regulator expressed in a range of cell types, including mucosal immune cells and the intestinal epithelium. Furthermore, the enzyme Cyp27B1, which transforms inactive vitamin D [25(OH)D3] into its active, VDR-binding form [1,25(OH)2D3], is expressed in a variety of immune cell types as well as the intestinal epithelium. The presence of such essential actors in diverse cells of the gastrointestinal tract shows that active vitamin D functions as a paracrine chemical whose levels are adjusted in response to local demands. Intestinal bacteria have been found to modulate the vitamin D axis in the gut, operating on both the intestinal epithelium and local mucosal immune cells. The expression of Cyp27B1, as well as the expression of several genes involved in innate immunity (e.g., antibacterial peptides, tight junction proteins, cytokines and their receptors), has been reported to be reduced in the intestinal epithelial cells of germ-free and antibiotic-treated mice, suggesting that the synthesis of active vitamin D by the "microbiota-dependent" Cyp27B1 enzyme may be a requirement for the proper development of local innate immunity. Probiotics and pathogenic microorganisms, on the other hand, have been demonstrated to alter VDR expression in different directions, with the former increasing and the latter lowering it. In an attempt to evade immune monitoring and modify host genes to promote their survival, viruses target VDR in particular. The VDR gene (VDR, 12q12-14) is one of the candidate genes that has been researched intensively for possible links to IBD. The risk of CD is enhanced in the presence of the VDR ApaI polymorphism and the TaqI tt genotype, whereas the risk of UC may be reduced in the presence of the VDR TaqI polymorphism, especially in Caucasians, according to the findings of two recent meta-analyses. The VDR FokI polymorphism has been linked to UC susceptibility in Asians. VDR knockout (VDR KO) mice were more susceptible to experimental colitis in animal models, as evidenced by worse histology scores, increased expression of proinflammatory cytokine genes, and the development of intestinal dysbiosis. The latter, in turn, has been shown to drastically alter the composition of bile acids in faeces, which could have a significant impact on future molecular communication, with a specific focus on immune-related cellular responses. Vitamin D binding protein (VDBP), also known as Gc globulin (human group-specific component (Gc)), is a 55-kDa serum protein released by the liver that transports active and inactive vitamin D in the plasma. It belongs to the albumin superfamily. SNPs in the VDBP gene have been reported to impact circulating amounts of this protein as well as circulating 25(OH)D3. VDBP is required for the proper operation of the endocytic pathway, which is required for the renal absorption of 25(OH)D3 into renal tubular cells and subsequent vitamin activation. Specific SNPs in VDBP (VDBP 420 variant Lys; 416 Asp 420 Lys) have been linked to IBD, albeit their exact role in pathogenesis is unknown. VDBP has proven that it can operate as a chemotactic and scavenger agent, as well as a macrophage activator, in addition to being a vitamin D carrier. Plasma VDBP, in fact, effectively scavenges G-actin produced at necrotic cell sites and prevents actin polymerization in the circulation. It also serves as a co-chemotactic factor for C5a, a highly potent chemotactic factor for all leukocytes and a variety of other cell types that are produced by restricted proteolytic cleavage of C5 during complement activation. VDBP is also changed into macrophage-derived macrophage activating factor (GcMAF) after stepwise modification of its sugar moiety, which not only has a completely active ingestion function and cytotoxic capability after 3 hours but also exhibits anticancer and antiangiogenic effects. As a result, cloned GcMAF constructs and GcMAF-mimicking peptides have been created for use as immunopotentiators in clinical trials.

The interplay of the vitamin D axis, gut microbiome and gut mucosal immune system at the intestinal level

The intestinal epithelial barrier, the gut microbiota, and components of the innate and adaptive immune systems all play a role in maintaining intestinal homeostasis, which is regulated by the interaction of several variables linked by complicated molecular signalling. The vitamin D axis has been shown to have interesting impacts on each of these components. The differentiated intestinal epithelium acts as a barrier between the intestinal lumen and the gut mucosa, preventing molecules from freely flowing between them. Indeed, the presence of adhesion structures between adjacent epithelial cells, such as tight junctions (occludin, zonula occludens proteins, and claudins), adherens junctions (E-cadherin, catenins, nectin), desmosomes, and gap junctions, ensures the sealing of the paracellular space and regulates mucosal barrier permeability. The integrity of the gut mucosa is also important for microbial protection. In fact, disrupting barrier function makes it easier to become infected with enteropathogenic bacteria and develop intestinal inflammation and IBD. In diverse models of intestinal inflammation, probiotics have been found to reduce paracellular permeability, as measured by transepithelial electrical resistance (TEER), as well as epithelial death. In the setting of several infectious and immune-mediated diseases of the lung (cystic fibrosis, interstitial lung disease, asthma, tuberculosis, chronic obstructive pulmonary disease), skin (atopic dermatitis), oral mucosa, and eyes, where impairment of the vitamin D axis has been described, impaired mucosal barrier function with hyperpermeability is also common. Furthermore, intestinal epithelial cells collaborate with hematopoietic compartments to regulate enteric infections and are critical in the beginning of type 2 immune responses. Paneth cells, goblet cells, and the specialised phagocytic, antigen-presenting M cells found in the follicle-associated epithelium overlaying organised lymphoid structures are all epithelial-derived immunocompetent cells. Vitamin D and its receptor defend epithelial barriers in a variety of organs, including the intestinal mucosa. In fact, active vitamin D has been shown to boost the expression of a number of tight junction and adherent junction proteins. At various anatomic sites, including the corneal epithelium, podocytes, and enterocytes, active vitamin D stimulates the expression and/or membrane translocation of occludin, the zonula occludens proteins ZO-1 and ZO-2, claudins 2, -7, and -12, and vinculin. In vitro studies showed that pretreatment with 1,25(OH)2D3 protects intestinal epithelial cells from dextran sulphate sodium (DSS)-induced increased permeability, and in vivo studies using VDR KO mice revealed increased susceptibility to DSS-induced colitis when compared to their wild-type littermates. Adherent proteins are active in signal transduction in addition to their sealing capabilities, and VDR can regulate such pathways by acting on VDR-regulated promoters. For example, by inducing E-cadherin and inhibiting -catenin signalling through the VDR, active vitamin D inhibits colon cancer cell proliferation and promotes differentiation. These findings support the significance of the vitamin D axis in the formation, integrity, and healing capacity of the mucosal barrier.

Intestinal microbiome

The Human Microbiome Project has generated unparalleled information about the diversity and function of microbial communities and their genes, sometimes known as the human microbiome, in recent years. The quantity and relative distribution of distinct microbial species defined health and disease states in people, according to the sequencing of microbial ribosomal RNA taken from various body regions; for example, decreased diversity in the gut was reported in IBD. The intestinal microbiome has a role in metabolism, mucosal barrier physiology, immunology, and inflammatory signalling, and its disturbance, or dysbiosis, is linked to the onset, maintenance, and perpetuation of a variety of intestinal and extraintestinal clinical disorders. Vitamin D and its receptor have been demonstrated to impact the makeup and functions of bacterial communities in the gut, protect from dysbiosis, and prevent IBD and its symptoms by modulating the expression of antimicrobial peptides, mucosal barrier function, and innate immunity. In the absence of vitamin D, downregulation of particular -defensins from ileal Paneth cells, as well as tight junction genes, was demonstrated to be a co-factor for dysbiosis in the setting of a high-fat dietary regimen, with subsequent endotoxemia and systemic inflammation. Pathogens may potentially use DNA methylation on specific sequences, such as micro-RNAs, to manipulate the monocyte/macrophage vitamin D axis in their favour (miRs). MiR-21, for example, can bind to CYP27B1 mRNA and inhibit its action, lowering the localised synthesis of active vitamin D in monocytes. Probiotics, which are ingestible non-pathogenic live microbes that can give some therapeutic benefits to the host when ingested in sufficient levels as food components, have been widely employed in clinical trials for the treatment of IBD, with mixed results. It was recently discovered that a fully functioning VDR pathway is essential for probiotic protection against colitis, which is relevant because VDR expression in IBD patients can be drastically reduced as a result of chronic inflammation or dysbiosis. In fact, compared to littermates, VDR KO mice did not respond to probiotics such as Lactobacillus rhamnosus strain GG (LGG) and Lactobacillus plantarum (LP) and exhibited worse Salmonella-induced colitis. In wild-type mice, the same probiotics were able to boost VDR expression and transcriptional activity, as well as antimicrobial peptide expression, and provide physiological and histologic protection from Salmonella-induced colitis. The interaction of the vitamin D axis with the gut microbiome is an exciting, yet understudied subject of research with therapeutic consequences.

Conclusion

Vitamin D's role in immunological-mediated disorders appears to be closely linked to bacterial metabolism, with chronic dysbiosis inducing VDR malfunction and setting off a vicious cycle in which a weakened immune system perpetuates disease. As a result, restoring VDR function at various cellular levels should be considered a therapeutic possibility. Probiotics and olmesartan have shown to be effective in this regard in animal trials, but further testing in human studies in specific therapeutic circumstances is required. In reality, little study has been done on the mutual effects of probiotics and vitamin D in people to far. 127 otherwise healthy hypercholesterolemic adults were assigned to take L. reuteri NCIMB 30242 or placebo capsules for a 9-week intervention period in a double-blind, placebo-controlled, randomised experiment. In comparison to placebo, oral probiotic supplementation resulted in a significant increase in circulation vitamin D (p=0.003). Olmesartan is an angiotensin-converting enzyme inhibitor that also binds to the VDR. According to some data, it functions as a VDR agonist, restoring appropriate VDR activity by displacing inhibiting bacterial products bound to the receptor. Olmesartan has been proposed as a treatment for autoimmune illnesses in combination with pulsed, low-dose, broad-spectrum, bacteriostatic antibiotics. By lowering IEC apoptosis, increasing epithelial VDR levels with vitamin D analogues or anti-TNF medication could be another way to alleviate IBD. Several VDR ligands with low calcemic effects but great therapeutic potential have also attracted attention as potential substitutes for active vitamin D. In fact, despite the fact that major side effects of vitamin D supplementation, such as hypercalcemia, have been reported infrequently and are usually only seen after exposure to high doses of the active hormone, the risk of vascular calcifications, hypercalciuria, and renal complications after long-term vitamin D exposure remains unknown. Finally, current breakthroughs in understanding in the fields of microbiomics and nutraceuticals have interesting implications in the treatment of immune-mediated disorders. Despite continuing gaps that hinder recommendations to include modulation of the vitamin D axis and microbiota in clinical practise guidelines, recent study findings urge the pursuit of this objective for better, focused therapy for patients with IBD.

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A New Treatment Strategy for Multiple Myeloma with Monoclonal Antibodies

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Abstract

The approval of the first two monoclonal antibodies in the treatment of patients with relapsed and refractory multiple myeloma was a watershed moment for the multiple myeloma community in 2015. Despite early setbacks, monoclonal antibodies targeting CD38 (daratumumab) and signalling lymphocytic activation molecule F7 (SLAMF7) (elotuzumab) for patients with multiple myeloma became available in the same year for patients with multiple myeloma. Phase 3 clinical trials of combination treatments containing daratumumab or elotuzumab, in particular, have shown efficacy as well as a low safety profile. These monoclonal antibodies for multiple myeloma can kill target cells through antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, antibody-dependent phagocytosis, and direct signalling cascade blocking. Furthermore, their immunomodulatory activities may inhibit the immunosuppressive bone marrow microenvironment while also restoring immune effector cell activity. We focus on monoclonal antibodies that have shown clinical efficacy or have potential preclinical anti-multiple myeloma actions that warrant further clinical development in our study. We review the mechanisms underlying these monoclonal antibodies' anti-myeloma activities *in vitro* and *in vivo*, as well as pertinent preclinical and clinical findings. Monoclonal antibody-based immunotherapies have already changed the therapy landscape for multiple myeloma and will continue to do so.

Keywords: Multiple myeloma • Monoclonal antibody • Immunomodulatory • Bone marrow • Immunotherapy

Introduction

Multiple myeloma is the second most prevalent hematologic cancer, defined by the growth of malignant plasma cells in the bone marrow and an excess of immunoglobulin synthesis [1,2]. The development of novel therapeutic agents such as the proteasome inhibitors bortezomib [3], carfilzomib [4,5], and ixazomib [6] or immunomodulatory drugs (IMiDs) such as thalidomide [7], lenalidomide [8,], and pomalidomide [9,10] has improved the clinical outcome of patients with multiple myeloma in recent decades. In newly diagnosed patients, the response rate and extent, progression-free survival, and overall survival have all increased dramatically since the introduction of these innovative medicines into myeloma therapy methods. Due to its characteristic pattern of remission and return, it remains a chronic and incurable disease in the majority of instances. Patients with refractory illness or who relapse following treatment with proteasome inhibitors and IMiDs have a very bad prognosis. As a result, alternative methods aimed at diverse mechanisms are urgently needed to overcome drug resistance and reduce disease relapse. Multiple myeloma's origin and evolution have been connected to distinct immune system deficiencies as our understanding of the disease's biology have improved. Malignant plasma cells have higher levels of programmed cell death ligand 1 (PD-L1) and lower levels of tumour antigens and Human Leukocyte Antigen (HLA) molecules, which have been associated with deficiencies in dendritic cell antigen-presenting capacity and immunological tolerance, respectively. In addition, the bone marrow microenvironment in multiple myeloma has been demonstrated to be immunosuppressive, offering a haven for malignant plasma cells to proliferate, migrate, survive, and acquire drug resistance. Secreted inflammatory cytokines have been shown to promote the proliferation of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), Tumour-Associated Macrophages (TAMs), and regulatory T-cells in previous studies (Treg). Bone marrow stromal cells, Osteoclasts (OCs), and plasmacytoid Dendritic Cells (pDC), as well as cytokines such as interleukin-6 (IL-6), Macrophage Colony-Stimulating Factor (M-CSF), interleukin-10 (IL-10), tumour necrosis factor-beta, C-C Motif Chemokine Ligand 2 (CCL2), and vascular endothelial growth factor (VE These findings imply that an effective anti-myeloma treatment will need not only targeting the malignant plasma cell but also restoring the anti-tumour responses of immune effector cells by disrupting inhibitory signals on effector cells and blocking tumour evasion. When compared to targeted small compounds, monoclonal antibody-based treatments that provide additional effector cell-mediated tumour killing mechanisms are effective cancer therapy options. Monoclonal antibodies can kill cancer cells by targeting specific surface antigens through a variety of effector-dependent and effector-independent ways. Until now, therapeutic monoclonal antibodies based on IgG1 have been engineered to cause effector-mediated tumour cell lysis, such as Antibody-Dependent Cellular Cytotoxicity (ADCC), Complement-Dependent Cytotoxicity (CDC), and/or Antibody-Dependent Phagocytosis (ADPC). Therapeutic antibodies, which are dependent on target antigens, can also hinder cell development, trigger apoptosis, or deliver a medication, radiation, or cytotoxic substance by blocking receptors. In addition, the Fc region of antibodies is vital in facilitating the death of cancer cells by activating particular immune cells (NK cells or cytotoxic T cells). The development of the anti-CD20 monoclonal antibody rituximab for the treatment of haematological malignancies was a watershed moment that opened up new avenues for targeted cancer immunotherapies. Because of the effectiveness of rituximab in treating B-cell lymphomas, researchers have been looking for new monoclonal antibodies to treat myeloma. Because only a tiny number of myeloma patients express CD20, rituximab is ineffective in most cases. In late 2015, the Food and Drug Administration (FDA) approved two monoclonal antibodies targeting CD38 (daratumumab) and SLAMF7 (elotuzumab) to treat patients with relapsed and refractory multiple myeloma after demonstrating promising preclinical and clinical activities. CD38 is a 46-kDa type II transmembrane glycoprotein with a short N-terminal cytoplasmic tail (20 aa) and a large extracellular domain (256 aa) found on the surface of immune system cells. When lymphocytes are activated, the intensity of CD38 expression increases, and it is detected in the majority of hematopoietic linage cells. It's found on a lot of lymphoid and myeloid cells, although it's not present in most mature resting lymphocytes. It promotes the synthesis of secondary messengers that influence Ca2+ mobilisation. The regulation of calcium homeostasis in CD38-expressing lymphocytes has been connected to CD38's biological activity. Furthermore, CD38 serves many but distinct biological functions as a bifunctional enzyme that synthesises and hydrolyzes cyclic ADP-ribose as well as a signal-transducing surface receptor. CD38-/- mice are healthy and free of histological or pathological defects. Nicotinamide adenine dinucleotide (NAD)+, the substrate for its ecto-enzyme activity (ADP-ribosyl cyclase), and CD31/PECAM are natural ligands for CD38. In lymphocytes, the binding of CD31/PECAM and CD38 causes tyrosine phosphorylation and downstream signalling events that control proliferation and cytokine release. Previous research on CD38 and multiple myeloma have demonstrated that this glycoprotein is expressed abundantly and uniformly in terminally differentiated normal and malignant plasma cells. Due to its high expression in a number of haematological malignancies, such as multiple myeloma, B- and T-Acute Lymphoblastic Leukaemia (ALL), Non-Hodgkin lymphoma (NHL), Acute myeloid leukaemia (AML), and Chronic Lymphocytic Leukemia (CLL), a role for CD38 in the pathophysiology has been proposed (CLL). Due to its participation in the generation of immunosuppressive adenosine, a recent study revealed that CD38 enzymatic activity may be linked to immunosuppression in patients with multiple myeloma (ADO).

Daratumumab, a human IgG1-kappa monoclonal antibody, was the first naked CD38 monoclonal antibody to be further developed for clinical application after preclinical investigations with cell lines and animal models revealed potential anti-myeloma effectiveness. Daratumumab (previously HumaxCD38) has been shown in preclinical tests to kill CD38-expressing lymphoma and myeloma cells by CDC, ADCC, ADCP, and induction of apoptosis after Fc receptor-mediated crosslinking with anti-human IgG1 secondary antibody. The mechanism of CDC cytotoxicity generated by daratumumab was not seen in other CD38-expressing cells such as human NK cells, B and T cells, activated T cells, or monocytes. When compared to malignant plasma cells from multiple myeloma patients, CD38 expression on the cell membrane of these cells is comparatively modest. Increased expression of complement regulating proteins on the surface membrane of these cells or the requirement for a certain threshold amount of antigen expression to activate CDC is two possible explanations for this therapeutic indicator. Daratumumab-mediated ADCC was observed in these cells as well as primary tumour cells, in contrast to CDC. Another study found that pretreatment of mononuclear effector cells taken from healthy peripheral blood donors with lenalidomide dramatically increased ADCC, which was linked to lenalidomide activation of NK effector cells. Daratumumab also showed substantial anticancer activity in immune-deficient mice with CD38-expressing xenografts, suggesting that daratumumab may mediate non-immune mediated anti-tumour effects in vivo. Daratumumab treatment rapidly depleted CD38 high-expressing immunosuppressive regulatory T cells (Treg) and B cells (Breg), as well as myeloid-derived suppressor cells, according to a recent correlative study using flow cytometry on bone marrow and peripheral blood samples from clinical trial participants (MDSC). Immune effector cells such as helper and cytotoxic T cells, on the other hand, increased in number. CD38 levels vary significantly among hematopoietic lineage cell subpopulations. When compared to normal T, B, NK, and monocytes, it is discovered to be expressed at much higher levels in Treg, Breg, and MDSCs. Daratumumab decreases these major immune inhibitory cellular components immediately, alleviating their suppressive immunological function and enhancing effector cell-induced tumour cell lysis, according to this study. Daratumumab monotherapy was given to strongly pretreated patients with relapsed or refractory multiple myeloma in phase 1-2 investigation (with a median of 5.5 lines of prior therapy, 75 percent refractory to lenalidomide and bortezomib). In the dose-escalation phase, 32 individuals were enrolled. Daratumumab was given at doses ranging from 0.005 to 24 mg/kg once a week for eight weeks. The maximum dose that could be tolerated was not attained. Daratumumab was given to 72 individuals in the expansion phase at doses of 8 mg/kg or 16 mg/kg. Patients who received 16 mg/kg of daratumumab had a higher overall response rate (36%) and a longer median progression-free survival (5.6 *vs*. 2.4 months) than those who got 8 mg/kg. The most common reported side effects in the dose-expansion group were infusion-related responses, which occurred in 71% of patients and were predominantly grade 1 or 2. Neutropenia was the most common hematologic side event, occurring in 12 percent of patients in the 16 mg/kg group. The results of this tiny clinical study showed that monotherapy with this medication had significant activity in patients who had no other treatment alternatives, leading to FDA approval in 2015. Daratumumab at 16 mg/kg was given to 106 individuals with multiple myeloma refractory to proteasome inhibitors and IMiDs (with a median of 5 lines of prior treatment) in the phase 2 SIRIUS investigation. Overall, 29.2 percent of people responded. The median progression-free survival was 3.7 months and the time to response was 1.0 month. Overall survival at 12 months was 64.8 percent, and median overall survival was 17.5 months. Infusion-related events were reported in 42% of patients, with the majority of these being grade 1 or 2. Anaemia (24 percent), thrombocytopenia (19 percent), and neutropenia (14 percent) were the most common grade 3 or 4 side events (12 percent). The findings of two phase 3 trials on combination studies have been released. 498 individuals with relapsed or refractory multiple myeloma (one prior line of therapy) were treated with bortezomib plus dexamethasone with or without daratumumab in the CASTOR study. Daratumumab's addition to the treatment regimen enhanced the overall response rate (82.9 percent *vs*. 63.2 percent, p 0.001), 12-month progression-free survival (60.7 percent *vs*. 26.9%), and median progression-free survival (not reached *vs*. 7.2 months, p 0.001). Thrombocytopenia (45.3%), anaemia (14.4%), and neutropenia (14.4%) were the most prevalent grade 3 or 4 adverse events recorded in the daratumumab group (12.8 percent). Infusion-related events were reported in 45.3 percent of daratumumab individuals.

Conclusion

Monoclonal antibodies that target specific multiple myeloma antigens are a significant step forward in the development of successful immunotherapies for patients with multiple myeloma. Monoclonal antibodies can produce immunomodulatory effects on immune cells in the bone marrow microenvironment by decreasing the function and number of immunosuppressive cells and restoring the tumour-killing activities of immune effector cells, in addition to various mechanisms mediated *via* FcR-expressing effector cells (ADCC, CDC, or ADCP). Such unique immunomodulatory effects may lead to deeper clinical responses and greater efficacy, as seen in recent large phase 3 clinical trials with daratumumab. Previous clinical trials have shown that monoclonal antibodies are an effective treatment option for patients with relapsed and refractory multiple myeloma who have been highly pretreated. These antibodies will dramatically enhance the prognosis when used alone or in combination with other anti-myeloma medicines, immune checkpoint inhibition, and vaccination techniques. Monoclonal antibodies are also good partners to combine with various anti-myeloma treatments in the search for better and more durable responses in patients with all stages of the disease, particularly in early disease when the immune cells are still functional. Monoclonal antibodies that have already been licenced for the treatment of relapsed and refractory myeloma are being thoroughly explored for their potential function as frontline therapies. Studies are currently underway and will be conducted in the future to determine which combinations are most effective at various stages of the disease. We should expect a revolution of the therapy landscape and an improvement in patient outcomes as novel monoclonal antibodies continue to be developed at a rapid pace.

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Optimization of fermentation parameters for enhanced APHE production from Streptomyces griseocarneus through submerged fermentation

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Abstract

Increasing resistance of microbes against antimicrobial drugs keep scientists busy in exploring novel and potent antibiotics. The present study is concerned with the production of antitumor antibiotic from Streptomyces griseocarneus NRRL B1068 using submerged fermentation technique. The antibiotic activity was tested against three test microorganisms including A. niger, E. coli and B. subtilis by agar well diffusion method. The production of antibiotic was enhanced by optimizing culture and physical conditions. Different culture media were screened and M1 medium consisting of (g/L), potassium dihydrogen phosphate, 3.24; dipotassium hydrogen phosphate, 5.65; hydrated magnesium sulphate, 1.0; and 1 ml stock solution of salts (ferrous sulphate, 0.1; manganese chloride, 0.1; and zinc sulphate, 0.1) supplemented with 7.5% glucose and 2.0% lysine was found best for antibiotic synthesis. Optimum temperature, pH and incubation period for the production of antitumor antibiotic were found to be 30ºC, 7.2 and 7 days, respectively. Seven days old inoculum in a concentration of 8% (v/v) was determined best for antitumor antibiotic production by Streptomyces griseocarneus NRRL B1068

Immuno-modulatory and antimicrobial activity assays reveal a link between the biological actions of these compounds and the length of their aliphatic chains. Thus, antibiotics with longer aliphatic chains exhibited improved antimicrobial and immune modulatory activities. APHE-3 inhibits the proliferation of lymphocyte in the presence of phytohemagglutinin by more than 50% at a concentration of 10~4 M while APHE-1 and APHE- 2 are less effective. This is due to the smaller size of APHE-3 being better able to bypass the membrane barrier of the cells (Fildago et al., 1992).The present study is aimed at the optimization of some critical parameters for the production of antitumor antibiotics from Streptomyces griseocarneus and having an insight into the production process for obtaining maximum titer of antibiotic for commercial productions.

Keywords: Streptomyces griseocarneus; Antitumor; Hydrated Magnesium Sulphate; Potassium dihydrogen Phosphate; Dipotassium Hydrogen Phosphate; Bacterial resistance; Antimicrobial activity; Fermentation; Sensitivity;

Biography

Abida Rafique has done her BSc (Hons) and MPhil in Microbiology from Government College University Lahore. She has completed an internship at Chughtais Lahore Lab (CLL) where she shadowed senior members of the department and took part in numerous investigations. With use of samples of faeces, urine and wound swabs, she prepared and viewed agar plates and microscopic slides which allowed her to acquire a greater knowledge about the variety of skills and methods required in a Microbiology laboratory. She has also done a two weeks' work at Shaukat Khanum Memorial Cancer Hospital & Research Center Lahore

Conclusion

The purpose of the study was to optimize the fermentation parameters for the APHE antibiotics Production from Streptomyces griseocarneus NRRL B1068. It is concluded that microorganism showed maximum titers of APHE antibiotics under the optimized conditions of submerged fermentation. The optimization of the process significantly enhanced the yield of APHE antibiotics. The microorganism showed antimicrobial activity against all the three microorganisms tested and it can be accomplished that Streptomyces griseocarneus NRRL B1068 acts as a promising source of antimicrobial agent in future.

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Commentary Article

Colon Cancer Neoadjuvant Chemotherapy

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Abstract

Although neoadjuvant chemotherapy is routinely utilised in the treatment of a variety of solid tumours, it is still understudied in the treatment of locally advanced colon cancer. Early treatment of micro-metastatic disease, the capacity to reduce local disease burden, potentially leading to more effective resections, and enhanced treatment tolerance are all advantages of this technique extrapolated from other disease locations. Large, randomised clinical trials are investigating approaches for accurate staging and safe administration of systemic treatment, but the available data are either not mature enough or have not demonstrated a convincing argument for adoption into standard practice, necessitating further investigation. Although surgical resection is commonly used to treat early-stage colon cancer, not all patients achieve long-term remission. Adjuvant chemotherapy with fluoropyrimidine, with or without oxaliplatin, is often used to improve cure rates, but its efficacy in the neoadjuvant situation is unknown. Preoperative chemotherapy has been shown to be safe and effective in various gastrointestinal cancers, but there is a scarcity of evidence from big, prospective randomised trials, despite the fact that several are now underway. The theoretical risks and benefits, logistical challenges, and available safety and efficacy evidence relevant to the use of chemotherapy in locally advanced colon cancer will be discussed in this study.

Keywords: Colon cancer • Neoadjuvant • Chemotherapy • Immunotherapy

Introduction

In 2018, colon cancer was responsible for almost 1.1 million new cancer diagnoses and over 550,000 deaths worldwide. Furthermore, colon cancer is the world's third-biggest cause of cancer-related death. Over 70% of patients will have localised or regional disease, which means that mesocolic excision is the greatest option for cure. Following surgery, a surveillance plan is usually established to detect early recurrence, which includes a scheduled history and physical labs, which may include tumour markers, imaging, and endoscopic examinations. Adjuvant chemotherapy can be explored for stage II cancer, according to the National Comprehensive Cancer Network (NCCN) recommendations, with greater evidence to support its use as staging increases due to depth of invasion and lymph node involvement, as in stage III disease. To lower the likelihood of disease recurrence, a fluoropyrimidine with or without oxaliplatin (depending on stage and presence of high-risk characteristics) is usually given. Even with adjuvant chemotherapy, the chance of colorectal cancer recurrence after five years can be as high as 25%. There has recently been a surge in interest in the use of neoadjuvant chemotherapy (NAC) in the treatment of colon cancer. Although there have been few prospective randomised clinical trials to far, retrospective investigations and small institutional trials have suggested that there may be some benefit. Other gastrointestinal cancers, such as oesophagal, gastric, and rectal tumours, have already been treated with NAC [1-3]. There are several theories on the potential benefits of locally advanced colon cancer (LACC). First, NAC may help to eliminate micro-metastatic illness earlier and reduce the size/stage of the main tumour. Increased R0 (margin negative) resection rates could result as a result of this. Surgical stress causes locoregional metastases in animal models; however, tumour cell shedding could be reduced during surgery by using cytotoxic debulking with NAC. Furthermore, several observational studies have indicated that preoperative chemotherapy is better tolerated, resulting in fewer delays. However, there are several dangers associated with neoadjuvant chemotherapy. Peripheral neuropathy caused by oxaliplatin is a common side effect of colorectal cancer adjuvant chemotherapy, to the point where significant clinical trials have looked into the usefulness of decreasing treatment times. If patients have inaccurate radiographic staging, moving treatment into the pre-surgical space could result in overtreatment of low-risk patients. Although NAC allows for disease biology surveillance and chemo-responsiveness assessment, postponing surgery in nonresponsive tumours may result in tumour growth, predisposing patients to obstruction and/or perforation, necessitating emergency surgery with substantial morbidity and death. The evidence for and against the use of neoadjuvant chemotherapy in locally advanced colon cancer will be discussed in this paper, with a particular focus on recent randomised clinical studies and the implications of molecular subtypes. All clinical trial stages including neoadjuvant chemotherapy treatment in non-metastatic colon cancer were searched extensively in the literature. PubMed, clinicaltrials.gov, and a review of all major conference abstracts were all used in this search.

Staging *via* radiography

The capacity to appropriately stage patients using imaging is a critical component of the optimal administration of NAC in the preoperative setting in colon cancer. Adjuvant therapy has always been recommended based on pathologic staging, which is the gold standard. However, due to projected tumour regression, pathologic staging becomes less effective in determining the need for adjuvant treatment after cytotoxic chemotherapy. In early investigations using computed tomography (CT) to stage LACC, radiologists correctly identified T and N staging in 60% and 62 percent of cases, respectively. The sensitivity and specificity for distinguishing T3/T4 vs. T1/T2 through tumour infiltration beyond the muscularis propria were 95 percent and 50 percent, respectively, in a pilot study for the FOxTROT clinical trial (described below). A major retrospective investigation of the National Cancer Database (NCDB) looked at 105,569 individuals with clinical and pathologic staging and found that the correlation for the T stage was 80% and the correlation for the N stage was 83 percent. With higher T and N stages, agreement increased, implying that early-stage disease is more difficult to accurately assess. Other modalities, including as MRI and CT colonography, have been studied for usage, but they have not yet replaced CT as the gold standard in this field, owing to expense and invasiveness. Understanding the role of each radiographic staging modality and when to utilise it can help improve diagnostic accuracy and ensure that patients get the right treatment for their condition [4,5].

Retrospective research

Arredondo et al. in 2013 were one of the first to report the possible benefit of neoadjuvant therapy in LACC. Between 2009 and 2010, they looked at 22 patients with stage III colon cancer who were given preoperative CAPOX (capecitabine 1000 mg/m2 twice daily on days 1-7, oxaliplatin 85 mg/m^2 on day 1 every other week)4. They received four further cycles of adjuvant CAPOX after resection. All of the patients had a radiographic response, with a median tumour volume reduction of 69.5 percent. During preoperative treatment, no disease progressed. At 14.4 months after surgery, the actuarial overall survival (OS) and progression-free survival (PFS) were both 100%. Between 2009 and 2014, 43 more patients were assessed using the same technique (infusional 5-FU was used in some cases). With a median start time of 71 days from chemotherapy to surgery, the majority of 65 patients (93.8 percent) completed planned treatment and no procedures were delayed. The CT scan revealed a 62.5 percent reduction in tumour volume. In 4.6 percent of patients, pathologic complete response (pCR) was observed. Although only 60% of patients received adjuvant treatment, the

five-year actuarial OS rate was over 95%. These findings served as the foundation for ELECLA (NCT04188158), a larger, randomised phase II research of neoadjuvant CAPOX in LACC that is now underway. Many of the retrospective evidence on neoadjuvant chemotherapy comes from patients with T4b illness, which is defined as a tumour that invades or attaches to nearby tissues directly. Following the addition of NAC as a treatment option in T4b illness to NCCN recommendations in 2016, two large retrospective reviews of national databases were published. Dehal et al. presented a retrospective review of 921 individuals who had neoadjuvant chemotherapy between 2006 and 2014 in the NCDB in 2017. To compare this cohort to a standard of care group treated with upfront surgery and adjuvant chemotherapy, propensity score matching was performed. In comparison to the adjuvant group, patients treated with NAC were younger, had higher-grade histology, and advanced clinical T stage, but less advanced N stage. Three-year OS was 74 percent in the T4b neoadjuvant cohort after a median follow-up of 3.6 years, compared to 66 percent following adjuvant chemotherapy (hazard ratio (HR) 0.7, 95 percent CI 0.56–0.87; p = 0.0002). After propensity score matching, this comparison remained statistically significant. There was no difference in survival between the T3 and T4a cohorts [6-8].

In 2019, data from the Netherlands Cancer Registry was used in a similar investigation. 149 patients with clinical T4 LACC treated with neoadjuvant chemotherapy were evaluated using propensity score matching. In contrast to the NCDB research, only 77 percent of those treated with NAC obtained R0 resection, compared to 86 percent of those treated with adjuvant chemotherapy (p=0.037).

Single-arm prospective studies

The feasibility of the NAC method in LACC has been tested in a number of prospective, single-arm investigations. If they had a KRAS, BRAF, or PIK3CA mutation, or if their mutational status was unknown, Jakobsen et al. enrolled 77 patients with high-risk T3/T4 colon cancer and assigned them to receive three cycles of CAPOX (capecitabine 2000 mg/m2 daily on days 1–14 and oxaliplatin 130 mg/m2 on day 1 every 3 weeks) if they had a KRAS, BRAF CAPOX with panitumumab was given to wildtype patients. Patients who would have received adjuvant chemotherapy based on pathologic response continued to receive CAPOX 5 rounds without panitumumab. They were observed if they were converted to a lower stage and did not fit the criteria for adjuvant treatment. The rate of conversion from a higher clinical-stage to a lower pathologic stage that no longer required adjuvant treatment was the primary goal. The wildtype group had a conversion rate of 42%, compared to 51% in individuals with a mutation, with three patients obtaining a complete response. The converted group had a 3-year DFS of 94 percent against 63 percent in the non-converted group (p = 0.0005). Liu et al. used a similar approach in a single-arm phase II trial assessing neoadjuvant CAPOX for patients with LACC shortly after. A total of 47 patients were enrolled, with 42 of them receiving two to four cycles of NAC (depending on response) prior to resection, followed by eight cycles of adjuvant chemotherapy. The overall clinical response rate was 70.7 percent, with one partial. response rate (PR) of 68.3 percent. Notably, three patients with perforation or obstruction required emergency surgery, but perioperative morbidity and death were modest. After the efficacy of triplet therapy with a fluoropyrimidine, irinotecan, and oxaliplatin in metastatic colorectal cancer was proven, a feasibility study in localised disease in the neoadjuvant setting was done. Twenty-three patients with stage IIIB colon cancer were given four cycles of FOLFOXIRI, then resection and either FOLFOXIRI or CAPOX for another six cycles. Tumor volume decrease was observed in 91.3 percent of patients (including one pCR), with 56.6 percent incurring grade 3–4 toxicities, albeit no significant surgical complications. One patient's surgery was delayed due to continued bone marrow suppression, while two patients progressed during neoadjuvant treatment. Because of toxicity, only 52.2 percent of patients completed all four cycles of neoadjuvant chemotherapy. The 2-year OS rate was 95.7 percent at a median follow-up duration of 28 months, with a 26.1 percent recurrence rate.

Therapy tailored to the individual

Immune checkpoint inhibition (ICPI) has been demonstrated to be effective in the treatment of metastatic colorectal cancer, and it was recently approved as a first-line treatment for patients with microsatellite instability "high" (MSI-H). Following results in other cancers, interest in using ICPI in the neoadjuvant setting for colon cancer has developed. Investigators recommended using ICPI in both dMMR and pMMR LAC in the exploratory NICHE project. They hypothesised that early stage pMMR colon cancer could be more effective than late stage because of the increased degree of T-cell infiltration in the former. Celecoxib was also added to the pMMR group, based on preclinical indications that it may work synergistically with ICPI and boost tumour-promoting inflammation. Patients were given a dual ICPI of ipilimumab (day 1) and nivolumab (days 1 and 15), followed by surgery six weeks after study consent. In this phase II trial, the key goals were safety and feasibility. The analysis included 20 dMMR patients and 20 pMMR patients out of a total of 21 dMMR and 20 pMMR patients. There were no delays in surgery, and adverse events were consistent with the medicines' reported side effect profiles. A pathologic response was observed in 100% of the dMMR cohort (60 percent had a pCR). A pathologic response was observed in 27% of the pMMR tumours (13 percent pCR). After resection, four patients (1 dMMR, 3 pMMR) received adjuvant chemotherapy. All dMMR patients were alive and well after a median follow-up of nine months. One pMMR patient had metastatic illness, which was treated with palliative chemotherapy, and another died unexpectedly. Patients are still being enrolled in this trial [8].

Conclusion

As more evidence becomes available, neoadjuvant chemotherapy will most certainly find a place in the treatment of locally advanced colon cancer. It will be required to use molecular characterization and radiographic response to figure out which populations are likely to benefit. It will also be critical to avoid operational delays in patients who have a low likelihood of responding to cytotoxic treatment. Outside of standard chemotherapy, combining innovative techniques with immunotherapy or other targeted drugs could provide considerable survival benefits, including a tailored approach. The generalizability of any of these techniques must be considered, particularly with a growing young adult cohort that may be suitable for treatment intensification and an elderly patient population that is older than the median age indicated in the aforementioned trials. With increased developments in diagnostic imaging, molecular characterisation, and clinical trial enrolment, neoadjuvant treatment of colon cancer has the potential to grow into a new standard of care.

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Research Article

Effect of Probiotics in the Treatment of Acute Watery Diarrhoea in Children Admitted to a Tertiary Care Hospital in Bangladesh: A Non-Randomized Prospective Clinical Trial

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Abstract

Objective: The study aimed to assess the efficacy of probiotics in the context of acute watery Diarrhoea and their effects on serum immunoglobulin in children.

Methods: Prospective clinical trial in children aged one month to 12 years hospitalized with acute watery Diarrhoea in Uttara Adhunik Medical College, and allocated to receive probiotics, antibiotics, or probiotics + antibiotics for 30 days in accordance with the standard treatment protocol of Diarrhoea. Clinical outcome measurements included duration of Diarrhoea and treatment adverse events. Stool culture and blood immunoglobulin were analyzed on days 0 and 30.

Results: 166 enrolled children were divided into three groups: Group A (probiotics), Group B (antibiotics) and Group C (probiotics + antibiotics) with 98 participants returning for a follow-up visit on day 30. All groups were comparable in their baseline characteristics. Causative organisms of Diarrhoea among final participants (N=98) were *Rotavirus* (69.4%), *E. Coli* (67.4%), multiple organisms (2 or more) (45.9%), *Campylobacter* (34.7%), *Vibrio cholerae* (20.4%), *Salmonella* (10.2%), *Shigella* (9.2%), and *Klebsiella* (1.0%). Fastest recovery occurred in Group A (3.03 ± 0.76 days; Group C: 3.80 ± 1.10 days; Group B: 4.11 ± 1.48 days; p=0.001). At follow-up, administration of probiotics was associated with presence of commensal *Lactobacillus* and *Bifidobacterium* in stool.

Conclusion: Inclusion of probiotics for treatment of acute watery Diarrhoea in children is effective, safe and results in shorter duration of Diarrhoea and faster discharge from hospital. Probiotics may provide future alternative prevention and treatment strategies in childhood Diarrhoeal diseases in Bangladesh.

Trial registration: CTRI/2020/04/024633, Date: 15/04/2020

Keywords: Lactobacillus • Bifidobacterium • Acute watery diarrhoea • Probiotics • Clinical trials

Introduction

Diarrhoeal disease is responsible for a substantial health-related burden on human society and remains the second leading cause of death in children below 5 years of age. In addition, it is also a major cause of considerable morbidity in children of all ages throughout the globe [1]. Diarrhoea consists in the symptomatic presentation of acute gastroenteritis, commonly caused by infectious agents, such as viruses (Rotavirus, Norovirus), bacterial pathogens (*Escherichia coli*, toxigenic *Clostridium difficile*, *Campylobacter jejuni* and *Vibrio cholerae*) and parasites. However, the most common cause of gastroenteritis in children, especially in young children aged 3-24 months, is rotavirus infection. Around 1.4 million of the 9 million child deaths reported in 2008 were due to acute Diarrhoea, with 49% of the deaths occurring in five countries, namely India, Nigeria, the Democratic Republic of the Congo, Pakistan and China. In 2010, in countries with Low and Middle Socioeconomic Status (LMIC), the incidence of acute Diarrhoea was estimated around 2.9 episodes per child annually, mostly affecting infants aged 6-11 months [2]. In Europe, the incidence of Diarrhoea in children up to 3 years of age ranges from 0.5 to 1.9 episodes per child per year. Furthermore, infectious agents, such as enteropathogenic *E. coli* (EPEC), may cause protracted Diarrhoea in children, increasing the risk of long-term morbidities. Wardlaw et al. (2010) have shown that early onset of Diarrhoeal episodes predisposes children to lasting disabilities, stunted growth, and impaired cognition and school performance [3].

Notwithstanding obvious improvements in the case management of Diarrhoea, including early administration of oral rehydration solutions, continued feeding, oral zinc, and antibiotics, Diarrhoea remains responsible for 1.5 million deaths annually, or 1% of deaths in children under 5 years [4][5]. Use of antibiotics is still highly prevalent even if inappropriate for the most part and responsible for the bulk antibiotic consumption in humans, and consequently for their contribution to the emergence of antibiotic resistance [6]. However, when antibiotic therapy is deemed necessary, it is useful to have an easily available, cost-effective, and safe method to prevent potential side effects associated with such treatment.

In recent years, the use of probiotics has gained increased popularity, even if the concept of using probiotics for prevention and treatment of some human illnesses has been around for more than a century [7]. The WHO defines probiotics as a "live microorganisms which, when administered in adequate amounts, confer a health benefit to the host" [5]. Such definition is echoed by both the International Life Science Institute (ILSI) and the European Food and Feed Cultures Association (EFFCA) [8,9]. In general, probiotics are beneficial bacteria that colonize and replicate in the human intestinal tract providing positive benefits to the host. Several clinical trials support the efficacy of certain probiotics in the prevention and treatment of various Diarrhoeal illnesses, with microorganisms such as *Lactobacillus, Streptococcus* and *Bifidobacterium* being frequently used [10]. The rationale for probiotic use in acute Diarrhoeal diseases is predicated on the assumption that they act against enteric pathogens via activation of immune

signaling pathways, produce factors against enteric pathogens, and operate by inducing the host to secrete anti-pathogenic factors [11]. To date, numerous studies assessing the efficacy and safety of various probiotic species and strains in preventing and treating childhood infectious Diarrhoea are available. The ESPGHAN/ESPID evidence-based guidelines for the management of acute gastroenteritis in children in Europe summarized data from several meta-analyses, and reported a significant effect and moderate clinical benefit of selected probiotic strains in the treatment of acute watery Diarrhoea (primarily rotavirus), mainly in infants and young children [12]. In a trial conducted by Guandalini, rotavirus-positive patients were treated with oral rehydrating solution, and *Lactobacillus GG* (LGG) administration significantly improved recovery [13]. A body of evidence suggests that probiotics are safe when used in healthy children, and effective in reducing the duration of acute infectious Diarrhoea [14].

In Bangladesh, no studies have been conducted so far using probiotics in the treatment of Diarrhoea in children, even though Diarrhoea is a significant health problem in Bangladesh. This trial was therefore designed to evaluate the role of probiotics in children with acute-onset Diarrhoea of all causes.

Materials and methods

Participants

This study was performed as a parallel-group, interventional non-randomized study with enrollment of pediatric patients according to eligibility criteria and being allocated to receive probiotic therapy (Group A), conventional antibiotic treatment (Group B), and probiotic + antibiotic therapy (Group C) during the period of April, 2020 to July, 2020 at the Pediatric Department of Uttara Adhunik Medical College & Hospital in Bangladesh. The investigators were not blinded to group allocation. The study protocol received approval from the Institutional Ethical Review Committee (Ref: UAMC/ERC/Recommend - 62/2018), and clinical trial registration was conducted (CTRI/2020/04/024633, date: 15/04/2020). Only patients whose parents or legal guardians were willing and able to give written consent were enrolled in the study, and consents were collected before administering any treatment and collecting data. Inclusion criteria were: children aged from 1 month to 12 years, both sexes, who were diagnosed with dehydrating acute watery Diarrhoea of less than 14 days' duration, patients with clinical signs and symptoms of dehydration as illustrated by the presence of thirst or eagerness to drink, sunken eyes, dry mouth and tongue, and loss of skin elasticity, children who retained their ability to take oral medications. Moderate Diarrhoea means having more than a few but not more than 10 Diarrhoea stools in a day. Mild Diarrhoea means having a few Diarrhoea stools in a day. Exclusion criteria were patients with a history of an episode of Diarrhoea in the month preceding onset of the present illness to exclude recurrent and persistent Diarrhoea, severe dehydration, severe malnutrition, Diarrhoea associated with another systemic illness (e.g., septicemia, pneumonia, urinary tract infection, otitis media), known hypersensitivity reaction to probiotics, and any child who received antibiotic therapy within 1 month prior to inclusion in study.

Protocol

Subjects fulfilling the inclusion criteria were divided into three groups, namely A, B, C, on the basis of their anticipated therapy. Patients who received only probiotics were designated as Group A. The dose regimen of giving probiotic was 2 capsules twice daily for 48 hours, then 1 capsule twice daily for 8 days and then 1 capsule daily (below 3 years of age) and 2 capsules daily (3 years to 12 years) till day 30. Each capsule contained *Lactobacillus acidophilus* (2 billion), *Lactobacillus bulgaricus* (1 billion), *Bifidobacterium bifidum* (1 billion) and *Fructo-oligosacharides* (as prebiotic) (100mg) (manufactured by Renata Pharmaceutical Ltd, Dhaka, Bangladesh). Attribution to Group A was predicated on the findings of stool culture and examination, whereby if a virus was detected and no pathogenic bacteria emerged then participants were assigned. Patients who were assigned to receive antimicrobial agents according to the standard treatment protocol in place in the hospital were included in Group B. Patients in Group C were those who received both antibiotics and probiotic therapy. All groups also received zinc supplements in standard dosages and hydration therapy with ORS. After initial correction of dehydration, children continued to receive ORS as maintenance therapy by matching stool volume and any other fluid losses until Diarrhoea ceased. Breast-fed children were allowed to continue breast feeding. Formula or animal milk or normal diet was also permitted. Parents had the option to withdraw their children from the study at all times. The final study cohort required continued enrollment through 30 days and returning for follow up. Data collected from participants were kept under strict anonymity.

Assessment during baseline and follow up

After enrollment, a complete clinical history was taken from parents or legal guardians and a thorough physical examination was conducted and findings were recorded. Socio-demographic information was collected from the parents using a semi-structured questionnaire. Blood for assessment of serum electrolytes (day 0) and for immunoglobulins (IgM, IgG, IgA,) (days 0, 30) were drawn from each subject and send to Clinical Biochemistry Laboratory of Uttara Adhunik Medical College for analyses. IgM, IgG, IgA concentrations in serum were measured by using ELISA N Antiserum to Human IgM, IgG, IgA kits according to the manufacturer's instructions (Dade Behring Marburg GmbH, Marburg, Germany).

Stool samples were obtained on day 0 before starting treatment and transported to the Microbiology Department of Jahangirnagar University and Uttara Adhunik Medical College for primary isolation and identification of bacterial enteric pathogens and on day 30 for the detection of *Lactobacillus and Bifidobacterium* in fecal samples. To culture and identify *V. Colerae, E. Coli, Salmonella, Shigella, Klebsiella*, and *Campylobacter*, the following media were used: Thiosulphate Citrate Bile Salts-Sucrose Agar (TCBS), Eosine Methylene Blue (EMB) agar, *Salmonella Shigella* (SS) agar, MacConkey agar, Campylobacter base agar with Campylobacter specific commercial supplements (Hi media, India). MRS agar was followed by gram staining for both *Lactobacilli* and *Bifidobacterium*. The Xpect™ *Rotavirus* test kit was used for the qualitative detection of *Rotavirus* antigens in human fecal specimens.

Rehydration

The degree of dehydration assessed clinically, was corrected and then fluid balance maintained using Oral Rehydration Solution (ORS) following WHO's recommended formulation and guidelines [19]. Briefly each child was given approximately 100 ml/kg of ORS during the first four hours. The ORS was administered in frequent sips using a spoon or by nasogastric tube. if vomit or stool output rates were high. After this period, ongoing fluid and electrolytes losses were replaced with the same solution on a volume-to-volume basis until Diarrhoea ceased.

Outcome measures

Clinical outcome measures:

- Rate of treatment failure: The proportion of children in every group who experienced recurrence or continued presence of signs and symptoms of Diarrhoea, worsening electrolyte abnormalities, or no weight gain from enrollment.
- Duration of Diarrhoea: Time from enrollment to passage of the last liquid stool.
- Occurrence of adverse events.

Laboratory outcomes:

Restoration of *Lactobacillus* and *Bifidobacterium* dominant gut flora.

Statistical analysis

All data initially were collected in pre-coded forms. Some inferential statistics (e.g., chi-square tests, fisher's exact tests, Kruskal Wallis test, etc.) were conducted to compare across treatment groups. Paired sample t-tests were also executed to investigate the effect of treatment on serum immunoglobulin during enrollment and follow up. Values were expressed as both frequencies (%) and mean (± SD). A two-tailed *p*-value <0.05 was considered to achieve statistical significance.

Results

A total of 166 participants were enrolled and allocated into the three groups as follows: Group A: n=64, Group B: n=41, and Group C: n=61. However, 68 patients had to be excluded from the study because of either parental unwillingness to participate during the study or because they did not return for follow-up. The final cohort includes therefore 98 children, with 30 patients in Group A, 38 patients in Group B, and the remaining 30 patients in Group C (Figure 1), and their characteristics are shown in (Table 1) and indicate that no significant differences were present on enrollment across the 3 groups. The clinical and serum electrolyte characteristics of the cohort are shown in (Table 2).

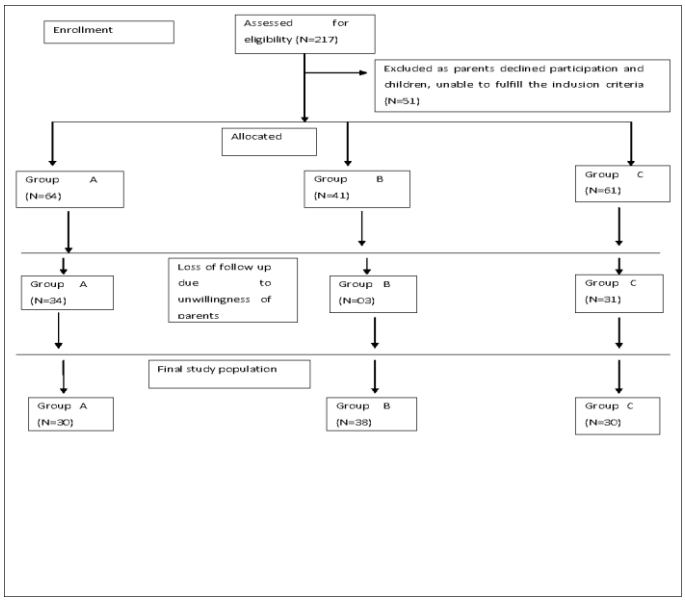

Figure 1. Flow chart of the study.

Table 1. Socio-demographic characteristics of the cohort based on treatment group allocation (n=98).

Variables	**Group A (Probiotics) (n=30) n (%)**	**Group B (Antibiotics) (n=38) n (%)**	**Group C (Probiotic + Antibiotics) (n=30) n (%)**
Sex			
Male	18 (60%)	25(65.8 %)	15(50%)
Female	12 (30.0)	13 (32.5)	15 (37.5)
Residence			
Urban	12 (40%)	23 (60.5%)	16 (53.3%)
Rural	18 (60%)	15 (39.5%)	14 (46.7%)
Economic status			
Poor	07 (23.3%)	06 (15.8%)	03 (10%)
Middle class	23 (76.7%)	32 (84.2%)	27 (90%)
	Mean ± SD (Median)	Mean ± SD (Median)	Mean ± SD (Median)
Age (months)	24.50 ± 34.70 -13	32.60 ± 35.64 -18.5	20.11 ± 16.41 -15
Mean duration of diarrhea prior to enrollment	3.50 ± 2.79 -2.5	3.39 ± 2.79 -2	2.37 ± 1.33 -2
(Note: SD = Standard deviation)			

Table 2. Clinical parameters and serum electrolytes of the cohort upon enrollment.

Clinical parameters	**Group A (Probiotics) (n=30)**	**Group B (Antibiotics) (n=38)**	**Group C (Probiotics + Antibiotics) (n=30)**
Loose watery stool	30 (100%)	38(100%)	30(100%)
Fever	8 (26.7%)*	34 (89.5%)	22 (73.3%)
Abdominal pain	1 (3.3%)	0	0
Nausea/vomiting	24 (80%)	28 (73.7%)	24 (80%)
Blood in stools	2 (6.7%)	5 (13.2%)	2 (6.7%)
Others (Convulsion, anorexia, feeding difficulty)	2 (6.66%)	3 (7.9%)	0
Laboratory features	Mean ± SD	Mean ± SD	Mean ± SD
Na^+(mmol/L)	139.43 ± 3.34	137.89 ± 3.80	139.67 ± 3.82
K^+(mmol/L)	4.18 ± 0.53	3.95 ± 0.49	4.29 ± 0.59
Cl^-(mmol/L)	104.4 ± 3.79	101.71 ± 3.74	103.57 ± 3.85
Co_2(mmol/L)	26.67 ± 1.27	27.26 ± 1.86	27.43 ± 1.68
(Note: SD = standard Deviation; * - p<0.05 vs. the other 2 groups.)			

Stool culture findings on admission are shown in (Table 3) for all 3 treatment groups. The distribution of enteric pathogens was similar across groups (*p*-not significant).

Table 3. Stool microbiological findings during admission to the study.

Organisms	**Group A (Probiotics) (n=30) n (%)**	**Group B (Antibiotics) (n=38) n (%)**	**Group C (Probiotics + Antibiotics) (n=30) n (%)**
E. Coli	24 (80%)	25 (65.8%)	17 (56.7%)
Campylobacter	11 (36.7%)	10 (26.3%)	13 (43.3%)
Vibrio	7 (23.3 3%)	7(18.4%)	6 (20.0%)
Salmonella	3(10.0%)	5 (13.2%)	2 (6.7%)
Shigella	1 (3.3%)	5 (13.2%)	3(10.0%)
Klebsiella	0	0	1 (3.3)
Rotavirus	21(70.0 %)	29 (76.3)	18 (60.0%)
No growth	1 (3.3%)	1 (2.6)	1 (3.3%)

Cessation of Diarrhoea occurred significantly fastest among Group A children (3.03 ± 0.76 days), followed by patients who received antibiotics + probiotics (Group C: 3.80±1.10 days) and slowest to recover were those in Group B (4.11 ± 1.48 days) (p<0.001); (Table 4).

Table 4. Duration of diarrhea after starting medications of all enrolled participants (N=98)

Groups	**(Mean ± SD)**	**Kruskal Wallis Test (*p*-value)**
Probiotic group (N=30)	3.03 **±** 0.76 days	0.001
Antibiotic group (N=38)	4.11 **±** 1.48 days	
Antibiotic + Probiotic group (N=30)	3.80 **±** 1.10 days	

After 30 days of treatment, stool analyses revealed significant differences among groups for the presence of *Lactobacillus* and *Bifidobacterium* (*p*<0.001); (Table 5). The changes in serum immunoglobulin levels for each of the treatment groups are shown in (Table 6).

Table 5. Stool culture findings during follow-up visit on day 30 for the cohort based on treatment group.

Treatment Groups	**Lactobacillus + Bifidobacterium**	**Campylobacter**	**No growth**
Group A (Probiotics) (n=30)	30 (100%)	0	0
Group B (Antibiotics) (n=38)	9 (23.7%)*	1 (2.6%)	28 (73.7%)

Group C (Antibiotics + probiotics) (n=30)	29 (96.7%)	0	1 (3.3%)
(Note: *- p<0.001 vs. the other groups)			

Table 6. Effect of treatment on serum immunoglobulin.

Groups	Immunoglobulins	Time frame of measurement			
		During enrollment (Day 0) (Mean ± SD)	During follow up (Day 30) (Mean ± SD)	Individual Change (Post-Pre) (Mean ± SD)	*p*-value
Group A (Probiotic) (N=30)	IgM (mg/dl)	86.93 ± 32.2	112.38 ± 25.32	25.45 ± 27.87	<0.001
	IgG (mg/dl)	695.4 ± 167.83	841.61 ± 164.79	146.21 ± 93.99	<0.001
	IgA (mg/dl)	132.55 ± 66.79	158.72 ± 57.80	26.17 ± 32.88	<0.001
Group B (Antibiotic) (N=38)	IgM (mg/dl)	81.71 ± 40.16	106.92 ± 23.48	25.21 ± 35.12	0.106
	IgG (mg/dl)	584.42 ± 167.9	808.72 ± 195.21	224.3 ± 172.88	0.014
	IgA (mg/dl)	166.79 ± 87.79	216.78 ± 69.17	50 ± 103.75	0.249
Group C (Antibiotic + Probiotic) (N=30)	IgM (mg/dl)	72.34 ± 28.94	102.08 ± 33.83	29.74 ± 40.55	<0.001
	IgG (mg/dl)	639.52 ± 124.66	787.14 ± 172.91	147.62 ± 135.32	<0.001
	IgA (mg/dl)	121.88 ± 63.27	172.19 ± 70.95	50.31 ± 43.5	<0.001

Discussion

In the present study, incorporation of probiotics in the treatment of acute watery Diarrhoea in children emerged as effective, safe and was associated with a shorter duration of Diarrhoea, leading to a faster discharge from the hospital. These findings support the institution of probiotic approaches as a routine component of the management of acute watery Diarrhoea in Bangladesh, while closely monitoring opportunities to further improve on such intervention while attempting to minimize the use of antibiotics in this context.

Before we discuss the potential implications of our study, some specific comments on the ancillary findings are worthy of mention. All groups were comparable in their baseline characteristics. Common clinical features of Diarrhoea were loose watery stool, nausea/vomiting, fever, blood in stool. Laboratory findings were overall comparable to those of Salazar-Lindo et al. in 2004 in Peru, except for bicarbonate levels which were higher in the present study, suggesting less severe dehydration status [15]. The most prevalent enteropathogens detected at the time of enrollment differed considerably from those of the trials conducted in India and Finland. In the Finish trial, Rotavirus accounted for more than 80% of Diarrhoeal cases [16], while in the study from India, *Rotavirus* (34.55%), *E. coli* (19.95%), no growth of pathogens (23.7%), *Vibrio cholera* (6.95%), and *Shigella* (2%) were reported. Thus, the greater diversity of etiologic agents and frequent co-pathogen associations as identified in the presemay reflect more accurately the findings occurring in LMIC.

In the current study, no treatment failures occurred, similar to the trial in Finland, in which all infants recovered within 5 days, and no treatment failure was reported [17]. We used *L. acidophilus, L. bulgaricus, and Bifidobacterium bifidum* as probiotic preparation in this trial, while Dubey et al. (2008) used strains of *L. Casei, L. bulgaricus, L. plantarum, S. thermophiles* for the treatment of *Rotavirus* associated Diarrhoea in children [18]. Narayanappa et al. (2008) showed that *Bifilac* (a combination of several probiotics) was safe and effective in patients with acute viral Diarrhoea [19]. Two different studies that were conducted with the aim to evaluate the efficacy of *L. rhamnosus* GG strain in acute watery diarrhoea in children showed inconsistent effects [20]. Furthermore, no beneficial effects of *Lactobacillus acidophilus* were observed in children suffering from acute Diarrhoea [21]. Probable explanations for the inconsistency of the findings across the multiple studies may include: (i) the fact that probiotic preparations and doses were not standardized in the Indian context; (ii) data generated in Western countries cannot be extrapolated to Indian or LMIC settings; (iii) the poor nutritional status of Indian or LMIC children may alter the responses to the probiotic interventions; (iv) different food habits may also affect the response to therapy; (v) the presence of a wide variety of both helpful and harmful intestinal microflora that may interfere with the efficacy of the treatment. Accordingly, the Indian trial showed that about 12% of patients had unresolved Diarrhoea and an additional 20% were classified as treatment failure mostly due to severe Diarrhoea. Findings of two more studies conducted also in India found similar results. In a randomized controlled clinical trial of *L. sporogenes* as probiotic in clinical practice on acute watery Diarrhoea in children, no treatment failures or adverse effects and complications were reported. However, the rate of treatment failure reported in a study conducted in Peru where *L. Casei* strain GG was used in the treatment of infants with acute watery Diarrhoea was 21.1% with LGG vs 18.0% with placebo.

We should also remark that the duration of Diarrhoea was significantly different among the three groups, indicative of a major beneficial effect of the probiotic intervention, particularly when in isolation and without the concurrent treatment with antibiotics. The duration of Diarrhoea in our study was comparable to that reported in two previous trials. Overall conclusions of a meta-analysis of 63 studies of probiotics involving more than 8,000 participants, mostly children, suggests that probiotics shorten the duration of Diarrhoea by ~24 hours with no evidence of adverse effect [22].

A few studies have demonstrated the presence of significant associations of probiotic species with altered gut microbiota composition. In our trial, stool analysis of participants at the 1-month follow-up revealed that *Bifidobacterium* and *Lactobacillus* were detectable and predominant among the majority patients treated with probiotics, while they were much less likely to be detected in those not treated with probiotics. If we assume that the presence such as probiotic strains is indicative of intestinal health and also signifies potential prevention of future Diarrhoeal episodes, then administration of probiotics during the acute Diarrhoeal episode may have long-term benefits that will need to be quantified in future studies. In experimental settings in rodents, a recent metagenomic analysis of 8-week-old Swiss mice fed a high-fat diet showed that treatment with a probiotic mixture of *Lactobacillus* and *Bifidobacterium* (*L. rhamnosus, L. acidophilus*, and *Bifidobacterium bifidum*) significantly altered the composition of the gut microbiota [23].

Similar work on obese mice revealed that several *Lactobacillus spp*., *Bifidobacterium* spp., and other coliform bacteria increased in the gut microbiota in mice with a high-fat diet treated with various *Lactobacillus* probiotic *strains (L. acidophilus IMV B-7279, L. casei IMV B7280, B. animalis VKL, and B. animalis* VKB) [24]. Studies have demonstrated that *Bifidobacterium* and *Lactobacillus* can inhibit harmful bacteria, improves gastrointestinal barrier function and *Bifidobacterium* alters the function of dendritic cells to regulate the intestinal immune homeostasis to harmless antigens and bacteria or initiate protective measures against pathogens [25-28]. Such basic studies have been somewhat corroborated by clinical trials as well. Indeed, a clinical study demonstrated that patients who received *L. plantarum* DSM 9843 showed the presence of *L. plantarum* in rectal samples of patients, along with reduced amounts of enterococci in fecal specimens [29].

In another study, analyses of the fecal microbiota of patients treated with a probiotic mixture of *L. acidophilus, L. plantarum, L. rhamnosus, Bifidobacterium breve, B. lactis, B. longum* and *Streptococcus thermophilus*. and analyses of the fecal microbiota of these patients revealed that the similarity of the microbial composition was more similar in probiotics-treated patients than that of the placebo group [30]. Another study analyzed the fecal microbiota of 6-month-old infants treated with daily supplements of *L. rhamnosus* (LGG), and showed an abundance of LGG and an increased index of evenness in the fecal microbiota of these infants, suggesting ecological stability [31].

Many probiotic bacteria have been tested for their immunomodulatory properties, especially *Lactobacillus sp.* and *Bifidobacterium sp* [32-35]. In our study, all children during follow-up on day 30 showed an increase of serum IgM, IgG, IgA antibodies with highest increase in serum concentration of IgG in patients treated with only probiotics. These findings may suggest that the elimination of pathogenic organisms and reestablishment of normal gut flora induce improvements in immune status. Indeed, a double blind, randomized controlled trial in healthy adults reported that oral administration of *Bifidobacterium lactis* Bl-04 and *Lactobacillus Acidophilus* La-14 changed the serum immunoglobulin concentrations compared with controls [36]. Shin et al. in a study in pigs also reported that administration of *L. plantarum* strain JDFM LP11 led to increased serum IgG was increased [37]. Oral introduction of *Bifidobacterium bifidum* was shown to enhance antibody response to ovalbumin and *Bifidobacterium breve* was shown to stimulate IgA response to cholera toxin in mice [38,39]. An increased humoral immune response, including an increase in *rotavirus* specific antibody-secreting cells in the IgA class, was detected in children with acute rotavirus Diarrhoea who received *L. rhamnosus* GG during the acute phase of Diarrhoea [40]. The mean serum rotavirus IgA antibody concentration at the convalescent stage was also higher in those individuals receiving *L. rhamnosus* GG [41]. In another trial, oral administration of *L. acidophilus*

LBKV3 strain as probiotic showed enhancement of IgG immunoglobulin levels, and regulation of gut microflora [42].

Limitations

To date, insufficient data justify the routine use of probiotics in Diarrhoea in Bangladesh. Although the sample size was small, this was the first clinical trial in Bangladesh, and provides initial support to expand these observations. However, we should also indicate that the present study has the following limitations: (a) It was conducted involving only a small population.; (b) It was conducted only in one tertiary care teaching hospital in Dhaka city; (c) It does not represent the whole pediatric population of Bangladesh; (d) it did not conduct an in-depth analysis of gut microbiome using metagenomic approaches. A continuation of this study involving a large number of patients (both children and adult patients) involving all age groups from all areas in Bangladesh (rural and urban areas) and addressing the current limitations will be required to provide more accurate and definitive recommendations.

Conclusion

In this study, administration of probiotics showed promise in becoming either an alternative or a complementary treatment option for acute watery Diarrhoea in the pediatric population. It was also shown that probiotics also helped to improve the immunity of children. As probiotics are already in use in many fermented products or in sue as over the counter supplements in many countries, there are no *a priori* major safety concerns. Randomized controlled trials that incorporate probiotics in the treatment of Diarrhoeal diseases may potentially lead to improved utilization of the traditional and virtually universally applied antimicrobial chemotherapy in Bangladesh. Probiotics may also provide effective prevention of Diarrhoea, as illustrated by the increased serum levels of immunoglobulins.

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