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An Old Drug, New Tricks: Ivermectin

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Abstract

Approximately 35 years after its astonishing discovery, ivermectin is one of the most significant medications in veterinary and human medicine for the management of parasitic infection. It was the joint recipient of the 2015 Nobel Prize in Physiology or Medicine.Although its activity on glutamate-gated chloride channels in parasitic worms is best described, knowledge of its mode of action is still lacking. Ivermectin resistance is increasingly pervasive in the field of veterinary medicine, however the mechanisms underlying resistance are still unclear. Here, we go into this versatile drug's background and application to world health. We question if ivermectin could have other mechanisms of action on parasitic nematodes based on recent investigations in a number of systems.

Keywords: Ivermectin • Veterinary medicine • Pathogens • Blood–brain barrier

Introduction

One of the most popular and well-known antiparasitic medications in both human and veterinary medicine is Ivermectin (IVM). The influence of IVM on human health has been spectacular up to this point, starting with a lucky discovery on a Japanese golf course and ending with a Nobel Prize. Contrary to the Mectizan Donation Program has relieved millions of individuals in the world's poorest countries of the burden of onchocerciasis (river blindness), and subsequently, lymphatic filariasis (elephantiasis), and established a precedent for the importance of public-private partnerships in global health. The mode of action of IVM in parasite species, despite significant investigation since its discovery over 35 years ago, is still unknown. [1].

The consequences for present and future control measures are also relevant, as are the mechanisms of resistance that enable some pathogens to survive treatment. IVM features an intriguingly broad selection of far beyond the endoparasites and ectoparasites it was designed to manage, affects in many different creatures. IVM, for instance, has been demonstrated to control blood sugar and cholesterol levels in diabetic mice, to limit the growth of cancerous cells, to hinder the replication of certain flaviviruses, and to decrease the lifespan of the main malaria and trypanosomiasis insect vectors.

Although there is obviously still much to learn about this flexible medication, the prospect of more long-term approaches for ongoing helminth-control programs and creative uses to enhance and democratize human health are strong reasons to study them this reason. In this article, we cover IVM's present applications and talk about new research that show a remarkable diversity of pharmacological targets across many systems. We discuss some significant yet unanswered issues with drug action and resistance mechanisms in parasitic nematodes, and we propose that recently developed, high-quality genomic resources for parasitic helminths are the best resources to address these issues.

Microbiologist Satoshi Omura took a soil sample in 1970 from a wooded area next to a golf club in Kawana, Japan, on Honshu's southernmost coast. A Gram-positive bacteria, sample NRRL 8165, a previously unidentified species of Streptomyces, was isolated and grown by Omura which, along with 50 other strains of Streptomyces thought to be peculiar in appearance or culture characteristics, was submitted to William Campbell at Merck to be tested for antiparasitic properties. Mice infected with *Nematospiroides dubius* (now known as *Heligomosoides polygyrus*) responded favorably to NRRL 8165 cultures, and the active ingredients were isolated, revealing a class of macrocyclic lactones. The bacterium Streptomyces avermitilis and these naturally occurring substances were given the names avermectins and averminous, respectively, to represent the worm-free circumstances they created.

Avermectin A1, A2, B1, and B2 are a mixture of four naturally occurring chemicals, each of which has two variations, a and b. The superscripts 1 and 2 relate to the presence of methoxy or hydroxy groups at position C5, respectively, as indicated by the designations "A" and "B." a double bond between C22 and C23 or, alternatively, a hydrogen at C22 and a hydroxy group at C23. Secbutyl is present at C25 in the "a" variations while isopropyl is present in the "b" variants. Avermectins of the "B" series exhibited the highest activity, however initial experiments revealed that all four avermectins displayed considerable efficacy against sheep gastrointestinal nematodes. These minute changes in chemical structure were found to have major functional ramifications.

Although most mammals have a large safety margin for IVM, some canines with a deletion mutation in MDR1, a Pglycoprotein involved in the blood-brain barrier, are vulnerable to neurological side effects. The term "endectocide" originated from IVM's effectiveness against both endoparasites and ectoparasites, and Merck & Co. brought this first medication of its kind to the animal health market in 1981. Nearly yearly releases of new IVM formulations for various livestock and domestic pet species made IVM the world's best-selling animal health product by the late 1980s. Since then, a number of derivatives have been created with considerable commercial success, including eprinomectin and selamectin (topical use for small animals with a broader safety margin than IVM in dogs with the MDR1 mutation).

The milbemycins are a family of Streptomyces-derived anthelmintics that also includes two other macrocylic lactones of significant economic use, moxidectin and milbemycin oxime. The primary analogies and contrasts between milbemycins and avermectins have previously been discussed. IVM's market has continued to be quite robust in the livestock sector, especially for the control of gastrointestinal roundworms, while it is also approved for the management of bovine lungworm and a number of other ectoparasites. The most widely used anthelmintics at the moment in the UK sheep industry and the US cattle business are IVM and other macrocyclic lactones. In the UK, these are also the anthelmintics that are most usually used to treat horses with roundworms. Additionally, a sizable market exists for macrocyclic lactones in the management of ectoparasites and parasitic nematodes in domestic pets. IVM has a license to treat canine heartworm, Dirofilaria immitis, and gastrointestinal roundworms in dogs when used with pyrantel. IVM, which is frequently used to prevent disease by focusing on the developing larvae after transmission from the mosquito, is ineffective against the adult stages of D. immitis. The key to IVM's value in endemic areas is that it is active during the first six weeks of infection against the L3,

L4, and juvenile adult worms without running the danger of the potentially disastrous effects of dead and dying mature adult worms in the heart. There was very little financial motivation to create IVM for the human health industry, despite the potential usefulness of IVM in the cattle and companion animal health markets being recognized from the beginning.

However, Dr. Roy Vagelos, CEO of Merck & Co., was inspired by IVM's effectiveness against the filarial nematodes that cause onchocerciasis and lymphatic filariasis to donate as much IVM (marketed as Mectizan) "as was needed, for as long as needed, to anyone who wanted it." Since 1987, the Mectizan Donation Program has authorized 1.2 billion treatments for lymphatic filariasis control and elimination (delivered with albendazole supplied by GlaxoSmithKline) and 1.4 billion treatments for onchocerciasis control and eradication. Onchocerca volvulus adults are not killed by IVM, but a single oral dose (150 mg/kg) administered annually decreases microfilarial production and halts the spread of the disease. Similar to this, IVM monotherapy for lymphatic filariasis is microfilaricidal but does not kill adult Wuchereria bancrofti; nevertheless, in this instance, the decrease of microfilaria formation is too transient to stop the spread of the illness. IVM is well controlled, nevertheless, when albendazole is used annually.

Mode of action

IVM is effective in treating a variety of parasite infections, although its exact mechanism of action is less well understood. IVM operates through glutamate-gated ligand-gated chloride channels to impact worm movement, feeding, and reproduction at nanomolar doses. Since glutamate-gated chloride channels are absent in vertebrates, they are believed to be responsible for IVM's extensive safety margin. GABA, glycine, histamine, and nicotinic acetylcholine receptors are just a few of the ligand-gated channels that IVM can interact with when present at micromolar concentrations in both invertebrates and vertebrates. The effect of IVM on worm motion and eating is likely related to binding to GluCls because it is expressed in nematode motor neuron commissures, lateral and sublateral nerve cords, and pharyngeal neurons. Native GluCls have a variety of subunit kinds, while functional GluCls are made up of five different subunit types. Six genes in the free-living nematode Caenorhabditis elegans encode GluCl subunits, with glc 1 serving as the main target of IVM. Even among closely related species, the GluCl family appears to be extremely diverse among parasitic worms. The human hookworms Necator americanus and Ancylostoma ceylanicum as well as the intestinal parasite of sheep, Haemonchus contortus, all belong to the same evolutionary group as *C. elegans,* but none of them have glc-1 orthologues.

However, functional GluCl channels can be produced from various combinations of subunits, and variations in the distribution and composition of the GluCl channels, as well as differential sensitivity of the other ligand-channel types, may affect how susceptible different nematode species are to IVM (remarkably, A. ceylanicum exhibits a susceptibility to IVM that is 40 times-300 times greater than that of *N. americanus*, according to *in vitro* and *in vivo* studies. The best evidence for this effect of IVM on nematode fertility comes from research on filarial worms, where it has long been known that IVM inhibits the development of microfilariae in utero. Following in vitro exposure to female Brugia malayi to 100 nM-1 mM IVM, alterations in gene expression have now been discovered using transcriptomic analysis, with differentially expressed transcripts being particularly enriched for those related in female reproductive. Up until recently, it was assumed that IVM had no direct influence on fecundity because no GluCls had been discovered in the worm reproductive tract. Avr-14, a GluCl component, was found in the *B. malayi* genome study, and it was localized to the adult Brugia's reproductive system using particular RNA probes.

An observation that may aid in characterizing avr-14's function is that it was most robustly expressed in the embryonic stages of microfilariae, the female worm's uterine wall, and to a lesser extent, the male reproductive tract. Similar to filarial nematodes, different stages of the parasite can be susceptible to IVM, and there is mounting proof that interactions with the host immune system influence the activity of IVM. An antibody against a peptide derived from AVR-14-A was utilized to specifically localize GluCl to the tissue surrounding the Excretory-Secretory (ES) apparatus in *B. malayi* microfilariae. It was believed that IVM might decrease the release of proteins from the ES vesicle, which would modify in vivo host immunological responses. This theory is supported by data from *D. immitis* microfilariae, wherein *in vitro* exposure to IVM increased the binding of neutrophils and peripheral blood mononuclear cells. Additionally, the in vitro effects of IVM for both *D. immitis* and *O. volvulus* microfilariae needed considerably greater doses than *in vivo*, confirming a role for host immune function in IVM activity.

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Insights from a Longitudinal Cohort Research on Young Adults' Non-Compliance with Public Health Initiatives Connected to Covid-19

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Abstract

International research has highlighted adolescents and young adults as a group with possibly low compliance rates with public health initiatives to stop the spread of coronavirus disease (COVID-19). Although research on non-compliance during pandemics has frequently concentrated on contemporary correlations, less is known about the relationship between non-compliance during pandemics and prior social and psychological risk factors. Public health campaigns should employ tactics that promote moral obligation and trust in authorities, or they should use reliable members of the community to spread information, in order to encourage voluntary compliance with COVID-19 policies. Self-monitoring, environment remodelling, or nudging may promote compliance in young adults with poor self-control. Investments made over time to reintegrate young people with antisocial tendencies into society may reduce rule-breaking, even during pandemics when adherence to the law saves lives.

Keywords: COVID-19 • World health organization • Sociodemographic

Introduction

International research has highlighted adolescents and young adults as a group with potentially low compliance with public health initiatives intended to stop the spread of coronavirus disease 2019 (COVID-19), particularly with social distancing initiatives. The World Health Organization [WHO] issued a specific call to young people for increased compliance in the middle of March 2020. This group is nonetheless contagious even if it frequently exhibits only minimal or no COVID-19 symptoms. Given that they also frequently have extensive social networks and active social lives, their potential for transmitting the virus is high. Research on noncompliance with preventative measures during this and prior pandemics has traditionally concentrated on proximal, contemporaneous correlates [1].

People who believe there is a high risk of catching the virus or being injured by it, who look for additional information, have faith in the government, and feel a moral need to obey, for instance, are more likely to take precautions. Higher education and some sociodemographic traits, including sex (i.e., female), have also been linked to increased compliance, but those from other demographic backgrounds may not have the practical capacity to comply because of their work or financial worries. The relationship between earlier social and psychological risk factors and non-compliance during pandemics is less well understood. New research indicates that impulsivity and certain personality traits, such as amorality, egoism, and psychopathy, are linked to non-compliance with public health measures connected to COVID-19.

Young people with "antisocial potential" traits—poor self-control, high delinquent behavior, high affiliation with delinquent peers, low moral rule acceptance, legal cynicism, and low shame or guilt—are more prone to breach the law in non-pandemic circumstances. This makes the traits that make people potentially antisocial strong candidates as indicators of those who won't follow through with steps meant to stop the virus from spreading. Using representative data that includes information on young people before and after the COVID-19 pandemic, it is best possible to determine whether earlier antisocial tendencies are related to subsequent non-compliance with COVID-19 public health measures. Thus, the current research makes use of a prospective-longitudinal study, whose data collecting started years before the pandemic and whose most recent data collection occurred in April 2020.

Young individuals reported their non-compliance with public health measures, as well as attitude and situational traits as risk-status, information seeking, and trust in the government, during the COVID-19 epidemic. These same participants were comprehensively profiled prior to the pandemic in terms of their sociodemographic traits and those that may lead to antisocial propensity during adolescence and early adulthood. We use the data to describe trends in young adults' non-compliance with COVID-19-related public health measures and to pinpoint the traits of adolescents and young adults that put them at higher risk for concurrent and future non-compliance. Data were gathered in Zurich, the biggest city in Switzerland.

Switzerland was among the ten most afflicted nations during the early weeks of the COVID-19 outbreak in Europe, with one of the highest per-capita infection rates. The initial public health advice were released on February 28; the first nationwide "lockdown" in Switzerland occurred from March 16 to April 26, 2020 [2]. Policies at the time prohibited social gatherings of more than five individuals, increased social distance, and keeping at home whenever possible. Government representatives and the Federal Office for Public Health broadly communicated consistent information and messaging about these public health initiatives through a variety of media (such as TV, radio, social media, poster campaigns, and the internet). Messaging was prominent in public areas (e.g., public transport). There were 25 different languages of information available on the virus and its limitations.

Literature Review

It is crucial to comprehend the traits of young people who disregard COVID-19-related public health measures if we are to create public health campaigns that are successful during the present and upcoming pandemics. In order to investigate the antecedent and concomitant factors connected with non-compliance, we used data from a longitudinal cohort research with assessments conducted before and throughout the COVID-19 pandemic [3]. The findings demonstrated that among a representative sample of young persons, compliance rates with COVID-19-related measures were relatively high and slightly superior than hygiene measures for social estrangement. Males, those with higher education levels, higher SES, and people without migrant backgrounds had greater non-compliance rates.

These relationships were primarily sparked by links to violations of hygiene-related laws. Analysis of antecedent and concurrent risk factors suggested that non-compliance was linked to a group of traits sometimes referred to as "antisocial potential": a low acceptance of moral rules, legal cynicism, a

low sense of shame or guilt, a low level of self-control, a high level of engagement in delinquent behaviors, and association with peers who exhibit social deviance. In the past, public health initiatives have used moral obligations and peer pressure to encourage compliance. Our findings back up these methods [4].

Some believe that the risk factors for being antisocial are less flexible in the near term, making them less amenable for intervention. Public health initiatives may not be able to significantly alter an individual's propensity for antisocial behavior in times of urgency, such as a pandemic, but they may be able to control the short-term consequences of some antisocial risk factors. For instance, evidence suggests that intervention strategies that try to address self-control deficits by self-monitoring, environmental restructuring, or nudging can reduce the effect of low self-control. Additionally, it appears from our findings that various mechanisms contribute to the habits of hygiene and social distance [5,6]. Negative attitudes toward authorities, such as a lack of confidence in the government and poor police legitimacy, for instance, were linked to social distance noncompliance but not hygiene noncompliance.

This has significant repercussions for public health programs and initiatives that seek to encourage adherence to COVID-19-related regulations. Compliance with social isolation measures necessitates a more drastic or limited behavioral shift, which has an immediate impact on one's psychological, social, and financial well-being. Without appropriate faith and belief that authorities are fair and effective in enforcing restrictive restrictions, adopting these behavioral changes may be seen as being excessively burdensome [7]. Additionally, trust may subtly encourage cooperation by raising a person's risk aversion. Our findings imply that some non-compliance hotspots need more attention from public health efforts. In general, there was little disregard for preventative practices including avoiding crowded areas, sneezing or coughing into one's elbow, and frequently washing one's hands. This suggests that the message was well spread and that young people generally welcomed these initiatives [8,9].

However, non-compliance with other hygiene and social distance measures like washing and disinfecting mobile phones or standing 1.5 m–2 m apart was comparatively greater. The lack of a "official" Swiss government advise to clean mobile phones may help to explain the lower levels of adherence to these hygiene precautions. International public health organizations and media organizations have nonetheless advised cleaning environmental surfaces, including mobile phones, as a preventative precaution against the virus's spread. These components of non-compliance should be addressed by public health initiatives, for instance by raising knowledge and comprehension of the virus on smartphones and other routes of transmission [10-12]. Last but not least, assessments of non-compliance by sociodemographic traits revealed that men are less likely to adhere to both cleanliness and social seclusion restrictions. Given that the research implies that COVID-19 death rates are higher for men than for women, this discovery is significant (Global Health 50/50, 2020). Additionally, our findings indicated that high SES and non-migrant young people were less likely to adhere to cleanliness standards, but not social distance measures.

Limitations

The current study has a number of advantages, but its measurements of social and psychological antecedent risk variables and widely representative sample stand out. One drawback is that the sample may not be typical of all of Switzerland or other nations. Furthermore, although Switzerland's COVID-19-related regulations are usually in line with international norms, there are significant policy and informational disparities that may contribute to noncompliance. For instance, while initially not advised in Switzerland, some nations and localities mandate the wearing of face masks when going outside. Furthermore, while information about the virus was disseminated by Swiss authorities with some consistency, messaging and implementation in other nations, like the United States, have been less centralized and uniform. Therefore, non-compliance with specific measures may differ depending on the regional public health campaigns and government recommendations [13]. Overall, our findings imply that during the first wave of the pandemic in Zurich, young people largely complied with COVID-19 public health measures. This high level of overall compliance may reflect the Swiss government's efforts to centralize information and regulations, but additional investigation is required to determine how public health campaigns and policy responses affect compliance internationally. Non-compliance was substantially correlated with diminished senses of moral obligation and poor levels of trust in authority, as well as traits indicative of prospective antisocial behavior. Public health campaigns can include tactics that promote moral responsibility and confidence in authorities, or they can use reliable members of the community to spread information. Our findings imply that it is crucial to put policies in place that target aspects of antisocial potential like self-control. This can be achieved, for instance, by encouraging protective health practices and behaviors through self-monitoring or environmental restructuring (sometimes known as "nudging") [14,15].

References

1. Pasrija, R., and Mohammad, N. "The deregulated immune reaction and cytokines release storm (CRS) in COVID-19 disease." Int. Immunopharmacol. 90 (2021): 107225.
2. Barari, S., et al. "Evaluating COVID-19 public health messaging in Italy: Self-reported compliance and growing mental health concerns." MedRxiv (2020).
3. Bults, M., et al. "Perceptions and behavioral responses of the general public during the 2009 influenza A (H1N1) pandemic: a systematic review." Disast med and public health prepared 9.2 (2015): 207-219.
4. Xu, Z., et al. "Pathological findings of COVID-19 associated with acute respiratory distress syndrome." Lancet respir. med. 8.4 (2020): 420-422.
5. Hirano, T. "IL-6 in inflammation, autoimmunity and cancer." *Int. Immunol.* 33.3 (2021): 127-148.
6. Harper, C A., et al. "Functional fear predicts public health compliance in the COVID-19 pandemic." Intern j of ment health and add 19.5 (2021): 1875-1888.
7. Tanaka, T., et al. "IL-6 in inflammation, immunity, and disease." Cold Spring Harb. perspect. biol. 6.10 (2014): a016295.
8. Folmer, C R, et al. "Compliance in the 1.5 meter society: longitudinal analysis of citizens' adherence to COVID-19 mitigation measures in a representative sample in the Netherlands." (2020).
9. Kaplan, S., et al. "Transit use reduction following COVID-19: The effect of threat appraisal, proactive coping and institutional trust." Transport Res Part A: Pol and Pract 159 (2022): 338-356.
10. Farooqi, F., et al. "Treatment of severe COVID-19 with tocilizumab mitigates cytokine storm and averts mechanical ventilation during acute respiratory distress: a case report and literature review." Trop. med. infect. dis. 5.3 (2020): 112.
11. Higgins, V., et al. "COVID-19: from an acute to chronic disease? Potential long-term health consequences." Crit. rev. clin. lab. sci. 58.5 (2021): 297-310.
12. Jeronimo, C., et al. "Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; Metcovid): a randomized, double-blind, phase IIb, placebo-controlled trial." Clin. Infect. Dis. 72.9 (2021): e373-e381.
13. Sheppard, M., et al. "Tocilizumab (actemra)." Hum. vaccines immunother. 13.9 (2017): 1972-1988.
14. Lan, S., et al. "Tocilizumab for severe COVID-19: a systematic review and meta-analysis." *Int. j. antimicrob. agents* 56.3 (2020): 106103.
15. Snow, T., et al. "Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials." *Intensive care med.* 47.6 (2021): 641-652.

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International Journal of Collaborative Research on Internal Medicine & Public Health 2023, Vol. 15, Issue 1, 001-002 Mini Review

Low-Dose Aspirin for Atherothrombosis Prevention

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Abstract

Atherosclerosis is a chronic inflammatory illness in which immune systems work with metabolic risk factors to start, spread, and activate vascular lesions. It is the main cause of ischemic coronary artery disease and cerebrovascular disease. Myocardial infarction or ischemic stroke may result from arterial thrombosis, an acute complication that appears on the surface of a torn atheromatous plaque or as a result of endothelial erosion. The growth and advancement of atheromatous plaques may be aided by platelets, which are important biological elements of arterial occlusive thrombi. Additionally, essential to hemostasis, the physiological procedure that stops bleeding following tissue trauma and vascular injury, are platelets. Although the adhesion and activation of platelets can be seen as a repair-oriented response to sudden fissuring or rupture of an atheromatous plaque, unchecked progression of such a process through a series of self-sustaining amplification loops may result in intraluminal thrombus formation, vascular occlusion, and transient ischemia or infarction. Due to their adhesive qualities and ability to quickly activate in response to a variety of stimuli, platelets can contribute in both healthy hemostasis and atherothrombosis. By selectively blocking important platelet enzymes or receptors, antiplatelet medications currently on the market interfere with specific steps in the activation process, lowering the risk of arterial thrombosis through mechanisms that cannot be separated from an increased risk of bleeding complications. Randomized studies specifically show that low-dose aspirin can prevent arterial thrombosis in a variety of situations, including the occurrence of first vascular events in low-risk, healthy subjects and the recurrence of vascular events in patients with known acute or chronic occlusive vascular disease. With a focus on the advantages and drawbacks in different patient populations, this review aims to reconcile our current knowledge of aspirin's molecular mechanism of action with the findings of clinical trials and epidemiological investigations.

Keywords: Pharmacokinetics • Atherothrombosis • Aspirin • Atheromatous plaques

Introduction

In the stomach and upper small intestine, aspirin is quickly absorbed mostly through passive diffusion of nondissociated acetylsalicylic acid through gastrointestinal membranes 30 minutes to 40 minutes after ingesting uncoated aspirin, plasma levels reach their highest. Contrarily, enteric-coated formulations can take up to three or four hours after administration for plasma levels to peak; as a result, patients should chew these medication if a quick antiplatelet action is necessary [1]. In the liver and gastrointestinal mucosa, esterases hydrolyze aspirin to produce salicylic acid. Regular aspirin tablets have an oral bioavailability of between 40% and 50% over a range of doses, whereas enteric-coated tablets and sustained-release, microencapsulated formulations have far lower oral bioavailabilities. Platelets first come into touch with aspirin in the portal circulation, which exposes them to far higher drug levels than those found in the systemic circulation. In plasma, aspirin has a half-life of 15 minutes to 20 minutes [2].

Despite aspirin's quick removal from the bloodstream, its antiplatelet effect lasts for the whole life of a platelet due to the irreversible inactivation of a crucial platelet enzyme. This effect can only be undone by producing new platelets. As a result, despite aspirin's extremely short half-life, its pharmacokinetics and pharmacodynamics are completely dissociated, allowing for the use of a once-daily regimen for antiplatelet therapy. The persistent inhibition of the cyclooxygenase (COX) activity of Prostaglandin H (PGH) synthase 1 and synthase 2, often known as COX-1 and COX-2, respectively, is the most well-known mode of action of aspirin5. These isozymes catalyze the transformation of arachidonic acid into PGH2, the first committed step in prostanoid biosynthesis. PGH2 is an unstable metabolic intermediate and a source of at least five distinct bioactive prostanoids, including Thromboxane A2 (TXA2) and prostacyclin, from numerous downstream isomerases (PGI2) [3]. Aspirin reaches the COX channel, a small hydrophobic passageway that connects the cell membrane to the enzyme's catalytic pocket, by diffusing through cell membranes. In order to block arachidonic acid from reaching the COX catalytic site of the enzyme, aspirin first binds to an arginine residue, which serves as a universal docking site for all Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). It then acetylates a serine residue (serine 529 in human COX-1 and serine 516 in human *COX-2*) in the channel's narrowest part. Aspirin must be taken in higher doses to block COX-2 than COX-1.7. These variations may, at least in part, explain why antiplatelet effects can be attained daily dosages as low as 30 mg of aspirin, whereas analgesic and antiinflammatory benefits require much greater doses [4].

Although mature platelets exclusively express COX-1, newly generated platelets express both COX-1 and COX-2. Vascular endothelial cells, on the other hand, express both COX-1 and COX-2. The latter is the main source of PGI2 in both health and sickness and is up-regulated in response to physiologic hemodynamics. PGH2 is converted largely into TXA2 and PGI2 by platelets and vascular endothelial cells, respectively. In response to various stimuli (such as collagen, thrombin, and adenosine diphosphate), platelets produce and release TXA2, which then interacts with a G-protein-coupled receptor called the TXA2 receptor to cause irreversible platelet aggregation. TXA2 thus offers a way for enhancing platelet responses to various agonists [5]. TXA2 is also proatherogenic, a strong vasoconstrictor, and it stimulates the growth of vascular smooth muscle cells. In contrast, PGI2 interferes with platelet aggregation by interacting with the PGI2 receptor in response to all agonists.

Additionally, PGI2 causes vasodilation, prevents vascular smooth muscle cells from proliferating, shields the heart from oxidative stress, and is antiatherogenic. The significance of PGI2 in vascular thromboresistance is supported by the finding that deletion of the gene encoding the PGI2 receptor is linked to an increase in susceptibility to experimental thrombosis. While *TXA2*, a prostanoid primarily formed from COX-1 (primarily from platelets), is particularly sensitive to aspirin's ability to suppress its manufacture, vascular PGI2, which is primarily derived from *COX2,* is less so. Induced by aspirin, platelets develop a long-lasting

functional impairment that can be identified clinically as an extended bleeding duration [6]. Low-dose aspirin, on the other hand, has no detectable effects on PGI2-dependent vascular functions; as a result, it has no influence on blood pressure, renal function, or the antihypertensive properties of diuretics and ACE inhibitors. Although alternative pathways have been suggested, platelet *COX-1* suppression alone is adequate to account for the antithrombotic properties of low-dose aspirin. Because platelet activation inhibition at sites of vascular injury may have indirect effects, such as reducing the release of inflammatory cytokines, oxygen radicals, growth factors, and other proteins, it is not necessarily implied that a single mediator, *TXA2*, is accountable for the 25% of major vascular events that can be prevented by lowdose aspirin in high-risk patients.

Additionally, the efficacy and security of low-dose aspirin are currently being studied in relation to other disease processes, which may be hampered, at least in part, by reduced release of these various platelet products. In fact, the idea that activated platelets cause the up-regulation of *COX-2* in one or more types of cells implicated in early intestine carcinogenesis is compatible with the effectiveness of once-daily regimens of low-dose aspirin in preventing the recurrence of colorectal adenoma [7].

Literature Review

Drug interactions

Low-dose aspirin therapy (75 mg daily) has no effect on blood pressure management or the requirement for antihypertensive medicine in patients with intensively managed hypertension, in contrast to treatment with the vast majority of *COX* inhibitors. This finding is in line with the fact that low-dose aspirin has no impact on renal prostaglandin synthesis [8]. In humans, constitutively expressed *COX-2* is necessary for renal prostaglandin production. The findings of a significant meta-analysis of myocardial infarction trials refute the hypothesis that aspirin may lessen the efficacy of ACE inhibitors after acute myocardial infarction. In patients with hypertension, there is no conflict between ACE inhibition and the cardioprotection provided by low-dose aspirin, and a meta-analysis of six long-term randomized trials comparing an ACE inhibitor with a placebo did not demonstrate that taking aspirin counteracted the positive effects of ACE inhibitors. Therefore, it would seem that ACE inhibitors are advantageous regardless of aspirin use.

The two-step method of *COX-1* inactivation has a pharmacodynamic interaction that may prevent aspirin from having its intended antiplatelet effect. The irreversible acetylation of platelet COX-1 by low-dose aspirin may be avoided by concurrent administration of reversible COX-1 inhibitors such ibuprofen and naproxen [9]. This is because these medications compete with aspirin for the same COX-1 channel docking site (arginine 120), which aspirin binds to with low affinity before acetylating serine 529. Coxibs and conventional nonsteroidal anti-inflammatory medications (NSAIDs), like diclofenac, which have some COX-2 selectivity, do not experience this pharmacodynamic interaction. Uncertainty exists on whether or not this interaction reduces or eliminates the cardioprotective effect of low-dose aspirin.

Upper gastrointestinal hemorrhage can result from aspirin therapy at low doses. Aspirin may lessen the gastrointestinal safety of selective *COX-2* inhibitors, in comparison to standard NSAIDs, according to subgroup analysis from two large trials. However, studies that compare selective *COX-2* inhibitors with conventional NSAIDs in individuals who have COPD need to investigate this potential interaction further. The inability of aspirin to decrease TXA2 production in vivo, to induce a meaningful response on ex vivo tests of platelet function, or to shield specific patients from thrombotic consequences has been referred to as "aspirin resistance."

Clopidogrel, a thienopyridine with an entirely other mechanism of action from that of aspirin, has seen similar effects. The factors behind interindividual heterogeneity in responsiveness to aspirin or clopidogrel are not covered by the word "resistance." In fact, it may be deceptive since itnot covered by the word "resistance." suggests that there is a measurable variable that directly affects clinical efficacy and that, based on the findings, may vary how antiplatelet medication is administered. The numerous ex vivo functional indicators of platelet capacity's relation to in vivo platelet activation, however, is mainly unclear. Additionally, there is we-ak connection between the outcomes of several aspirin responsiveness tests. 57 Therefore, we believe that the term "resistance" ought to be dropped. Instead, it is important to investigate the various elements that contribute to interindividual variation in response to aspirin or clopidogrel. These include the above-mentioned pharmacodynamic interaction with reversible *COX-1* inhibitors as well as the function of extraplatelet sources of *TXA2* synthesis in various clinical contexts for aspirin. Vascular events are common among patients on aspirin or other antiplatelet medications, just like with any medication meant to prevent atherothrombosis; this phenomenon is sometimes referred to as treatment failure. It is not unexpected that fewer than a quarter of all vascular complications may normally be avoided through the adoption of any one therapy given the multivariate nature of atherothrombosis [10].

Since we cannot be certain that a second vascular event in the same patient will share the same causative mechanisms as the first, there is no scientific justification for altering antiplatelet therapy in the face of such treatment failure. Furthermore, there isn't any solid proof that switching up the course of treatment is a better course of action than sticking with an antiplatelet regimen based on research. It may be possible to provide better patient care than requesting pointless tests of platelet function if there is a greater understanding of the elements that may conflict with the desirable antiplatelet effects of aspirin or clopidogrel, notably preventable medication interactions. To evaluate the antiplatelet effects of aspirin or clopidogrel in specific patients, no platelet function test is currently advised [11].

Efficacy and safety of low-dose aspirin in the prevention and treatment of atherothrombosis in high-risk patients

Aspirin's effectiveness and safety have been examined in a variety of populations, including individuals presenting with an acute myocardial infarction or an acute ischemic stroke and seemingly healthy people at low risk. According to individual studies and a metaanalysis of antiplatelet therapy trials, aspirin and other antiplatelet medications reduce the risk of a serious vascular event (nonfatal myocardial infarction, nonfatal stroke, or death from vascular causes) in patients with occlusive vascular disease by about 25%. This number reflects a combined 34% decrease in nonfatal myocardial infarction rates, a 25% decrease in nonfatal stroke rates, and a one-sixth decrease in nonfatal deaths from vascular or other causes. The absolute advantages of aspirin in specific patients can be assessed by lowering the projected absolute risk of nonfatal myocardial infarction by one because each of these proportional reductions applies uniformly to all groups of patients with vascular disease.

Third, the chance of a nonfatal stroke increased by a quarter, and the risk of vascular causes of death increased by a sixth. Aspirin normally avoids at least 10 to 20 fatal and nonfatal vascular events for every 1000 patients treated for a year among a variety of individuals with vascular disease, in which the annual risk of a serious vascular event varies from 4% to 8%. The risk of significant extracranial bleeding most commonly upper gastrointestinal bleeding roughly doubles with long-term therapy with low-dose aspirin, according to observational studies and a meta-analysis of randomized clinical trials in high-risk patients. This translates to an estimated absolute excess of 1 to 2 serious bleeding problems per 1000 patients receiving low-dose aspirin treatment for a year in middle-aged individuals. In addition, there are 1 to 2 hemorrhagic strokes per 10,000 patients in absolute excess.

Therefore, for the majority of high-risk patients taking low-dose aspirin, the likelihood of preventing a serious vascular event clearly outweighs the likelihood of preventing a major bleeding episode, unless a patient has an increased risk of bleeding due to advanced age, a history of ulcer, or concurrent treatment with other medications. Aspirin for patients at high risk for occlusive vascular disease has been approved by the Food and Drug Administration due to the aspirin's good risk-benefit ratio in high-risk patients, which led to level 1 recommendations. Cardiovascular registries and a recent survey suggest that aspirin use is not ideal despite this suggestion. A frequent justification for avoiding long-term aspirin treatment in high-risk patients is a history of negative aspirin reactions [12].

Treatment with a proton-pump inhibitor dramatically decreased the rate of heartburn, but not other aspirin-related symptoms, in a double-blind, placebo-controlled, randomized study including 150 patients using low-dose (80 mg daily) aspirin with upper gastrointestinal symptoms. Aspirin is a seldom occurring trigger of unpredictable hypersensitivity reactions, also known as "aspirin allergies," in addition to producing gastrointestinal discomfort. It may be possible to continue using this life-saving medication with proper classification of aspirin-allergic individuals and prompt referral of such patients to allergy services for potential desensitization.

In all clinical situations where antiplatelet prophylaxis has a good risk-benefit profile, aspirin is therefore advised. Considering that aspirin has the potential to reduce endothelial thromboresistance and gastric cytoprotection in a dosage-dependent manner, doctors are advised to take the lowest dose of aspirin that has been proven to be efficacious in each clinical situation. The evidence that is now available supports the use of daily aspirin doses between 75 mg and 100 mg for the long-term prevention of severe. Due to interindividual heterogeneity in the platelet turnover rate, which is a key factor in determining the intensity and duration of platelet inhibition on repeated low-dose aspirin administration, it is preferred to adopt a once-daily regimen rather than an every-other-day regimen. A loading dose of 160 mg to 200 mg should be administered at the time of diagnosis in clinical settings where an immediate antithrombotic effect is required (such as in the presence of acute coronary syndromes or acute ischemic stroke), in order to ensure rapid and complete inhibition of thromboxane-dependent platelet aggregation [13].

Discussion

Antiplatelet therapy could be enhanced in a number of ways to better prevent atherothrombosis. One crucial goal is to make sure that high-risk vascular disease patients utilize aspirin (or another effective antiplatelet regimen) as widely as is necessary. Many people who could benefit from low-dose aspirin are not routinely receiving it, according to several surveys; significant work is required to change these figures. There is a need for further placebo-controlled trials in specific patient groups because there isn't enough evidence to support the efficacy and safety of aspirin in some populations.

For instance, the Aspirin in Reducing Events in the Elderly trial and the current A Study of Cardiovascular Events in Diabetes should both provide useful evidence about the effectiveness and safety of aspirin in people with diabetes who have no history of vascular events regarding patients who are over 70.

It is legitimate to wonder if an alternate antithrombotic regimen would be more successful than aspirin in high-risk individuals who are already taking aspirin. Adding a second antithrombotic agent (either an antiplatelet or an anticoagulant) to aspirin is likely to result in significantly higher reductions in risk than switching from aspirin to an alternative agent, even though clopidogrel may be slightly more efficacious than aspirin in some high-risk categories. The use of this method is supported by some data from randomized trials, but further research is needed to determine its effectiveness and safety in various high-risk populations [14].

References

1. Hansson, G. K. "Inflammatory mechanisms in atherosclerosis." *J of Thromb and Haemos* 7 (2009): 328-331.
2. Ruggeri, Z M. "Platelets in atherothrombosis." *Nat med* 8.11 (2002): 1227-1234.
3. Patel, J. A., et al. "ASPIRIN RESISTANCE: MOLECULAR MECHANISMS & TECHNIQUES." *Intern J of Pharm Scien and Res* 2.7 (2011): 1623.
4. Pedersen, K., and Garret A. "Dose-related kinetics of aspirin: presystemic acetylation of platelet cyclooxygenase." *New Eng J of Med* 311.19 (1984): 1206-1211.
5. Weksler, B., et al. "Differential inhibition by aspirin of vascular and platelet prostaglandin synthesis in atherosclerotic patients." *New Eng J of Med* 308.14 (1983): 800-805.
6. Loll, J., et al. "The structural basis of aspirin activity inferred from the crystal structure of inactivated prostaglandin H2 synthase." *Nat struct boil* 2.8 (1995):

   643.
7. Barari S, et al. "Evaluating COVID-19 public health messaging in Italy: Self-reported compliance and growing mental health concerns." *MedRxiv* (2020).
8. Bults M, et al. "Perceptions and behavioral responses of the general public during the 2009 influenza A (H1N1) pandemic: a systematic review." *Disas med and public health* 9.2 (2015): 207-219.
9. Xu Z, et al. "Pathological findings of COVID-19 associated with acute respiratory distress syndrome." *Lancet respir. med.* 8.4 (2020): 420-422.
10. Hirano T. "IL-6 in inflammation, autoimmunity and cancer." *Int. Immunol.* 33.3 (2021): 127-148.
11. Harper C A., et al. "Functional fear predicts public health compliance in the COVID-19 pandemic." *Int j of mental health and add* 19.5 (2021): 1875-1888.
12. Tanaka T, et al. "IL-6 in inflammation, immunity, and disease." *Cold Spring Harb. perspect. biol.* 6.10 (2014): a016295.
13. Folmer C R, et al. "Compliance in the 1.5 meter society: longitudinal analysis of citizens' adherence to COVID-19 mitigation measures in a representative sample in the Netherlands." (2020).
14. Kaplan S, et al. "Transit use reduction following COVID-19: The effect of threat appraisal, proactive coping and institutional trust." *Transport Res Part A: Pol and Prac* 159 (2022): 338-356.

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A Case Study of Refractive Error on School-Going Children in the Selected Rural Area of Bangladesh

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Abstract

Refractive error is one of the most common causes of visual impairment around and it is quite common among school-going children. Children of age 04 years-15 years are a large number portions of the country in a rural area but few studies on such ground had been carried out previously. The aim of this case study was to find out the prevalence of refractive error and its associated factors among school-going children of age 04 years to 15 years. On the basis of 631 samples, the prevalence of refractive error was found 16%. Among the total study subject, more than 50% belong to the age group 7 years-9 years with mean age of 7.4 (± 3) years. Refractive error was significantly associated with gender (p=0.0037), duration of using smartphone (p=0.0113), the problem with headache (p=0.0001), and the problem with vomiting (p=0.0001). The majority of students were never examined for visual acuity, children should be examined at the time of entering school and when they are leaving, at least twice during their study period.

Keywords: Refractive error • Treatment facilities • Myopia • Durgapur upazila

Introduction

Refractive error is the second leading cause of treatable blindness and one of the significant causes of visual impairment [1]. To the preventable blindness, World Health Organization (WHO) has given first priority to refractive errors [2]. WHO given the strategies identified in their publication" Vision 2020 of a global initiative for the Elimination of Avoidable Blindness by 2020" [3], this severe information was presented as the obstacle to the effective national planning and the implementation of any eye care services. The global major challenge to work relentlessly to stops preventable blindness. The government and private sectors are both required to allocate more budgets to increase significantly the development of eye care services [4]. According to the WHO information before the one-decade refractive error was in Taiwan is 0.6%, Singapore is 0.5%, Indonesia is 2.2%, India is 4.3%, Malaysia is 0.3%, Bangladesh is 1.5% [5]. The refractive error was 0.5% responsible for economic blindness and 1.1% responsible for legal blindness (less than 6/60) [6]. In a study that was conducted in New Delhi, they found the refractive error was the cause in 81.7% of eyes with vision impairment [7]. The socio-economical loss due to childhood blindness is huge and human suffering is more. Including blind children, almost 80% of the global blind population lives in developing countries [8]. Bangladesh is one of the small developing countries and 40% of the estimated population is children [9]. As the healthcare facilities in the rural areas are inadequate in Bangladesh and under 15 year ages populations are at high risk in consideration with the refractive error. People are living in undervaluing are where the treatment facility is very low and may have a higher rate of visual problems. Khan et al. conduct a study on the refractive error among school-going children in rural areas of Bangladesh in 2004. In their study, 8.24% of boys and 9.01% of girls were selected from the study area, and recommend that this refractive error of this study is very much ignored [10]. Durgapur Upazila in Rajshahi district is one of the most populated Upazila and 96% of people are living in rural areas of that Upazila. Basically, the population of the Upazila is living in the poorest condition and they are facing problems getting medical and health facilities.

Although several studies have been conducted in the last decade in South Asian countries like India, Pakistan, and Bangladesh which could provide some scenario of such a problem in this region, but a little bit in lest developing country rural area like Bangladesh. The main objective of the study was to determine the prevalence of refractive errors and the associated factors among school-going children age 04 years to 15 years.

Material and Methods

This cross-sectional study was conducted to determine the prevalence of refractive error in school-going children. The sample size for the study was 630 which calculated using the appropriate formula with a 5% non-response error.

The data of 631 children age 04 years to 15 years have been collected from selected schools at Durgapur Upazila in Rajshahi District Bangladesh. Rajshahi District in Bangladesh consists of 9 Upazilas, Durgapur Upazila is one of them and the most populated Upazila of this district. The estimated population of the Upazila around 3,32,000 and among them 96% of people lives in rural areas. There are 74 primary and high schools for grade 1-10 classes' students. Firstly, Durgapur Upazila divided into 4 different locations with respect to their geographical locations. A complete list of all schools from primary to higher was collected and then four schools in each location were selected using a random digit table. All selected schools were visited to get the complete list of all students than subjects were selected by random sampling technique.

The study period was 1st February 2021 to 31st July 2021 with written ethical permission was obtained from Bangladesh Medical Research Council (BMRC), Bangladesh as well as verbal consent was obtained from teachers and study subject.

The information regarding age, gender, problems of the eye, vision, etc. were recorded and the color card and pinholes were also utilized. World Health Organization (WHO) criteria of visual acuity<6/18 were taken as visually impaired while<3/60 was taken as blindness [11]. Generally, the visual acuity of 6/12 does not affect school performance and hence is not considered as visually impaired in the current international literature. The screening procedures and related tools for this study developed by the PHeaRTS team as well as provide training to the staff that can perform the screening. Then they were received hands-on training from the ophthalmologist of the health Centre on how to perform refractive screening or vision screening for the school students. They collected data on knowledge of vision screening, eye diseases, and its care before the training. After the one-week training, the trainer collected the data to see the development of their capacity to perform more accurate standards as an eye nurse. The trained staff and teachers were performing the screening of refractive error in a team. Where 1 school teacher and one trainee work jointly.

Following variables were selected for the study, beside the socioeconomic and demographic factors; Fathers and mothers' occupations, joint or nuclear family status, have color identification problem or not, have any reading or watching problem or not, faces any headache or not, facing any problem of vomiting or not, facing any problem of squint eye or not and smartphone using status.

A pretest was conducted for the final preparing the questionnaire before the final implementation. Collect the information from the selected participant were face to face interview. After collecting data, it had been checked and verify to make sure that all study subjects are the answer to each item or not which one properly fulfill all questions of the questionnaire only those study subjects had been properly recorded for the data analysis. Statistical software SPSS version 16 used for data analysis.

Frequency tables were used to describe the distribution of the socio-educational characteristics of the study subjects. Chi-square test was used

to determine the association of the refractive error with respect to age, gender, father occupation, types of families, Body Mass Index (BMI), the problem with headache, and smartphone using status. And p-value<0.05 was considered significant.

Results

Socio-demographic and background characteristics of the study subjects

A total of 631 study subjects sincerely provided the information. Among them, 223 (35.34%) were less than 6 years, 317 (50.24%) from age 7 years to 9 years, and only 6(0.95%) were more than 12 years. Most of the study subject's father's occupation was farmer 231(36.61%), and daily labor 297(47.07%), as well as they, live in the joint family 442 (70.05%). Among the total study subject, only 423 (67.04%) study subjects were able to watch Television closely (<5 fits) and the rest of the others 208 (32.96%) were not able to watch Television closely. Total 197 (31.22%) study subjects were problems with headaches, and other study subjects are free from headaches 434(86.78%) as well as 25 study subjects were facing problems reading words on the blackboard (3.96%). Among all study subjects only 3(0.48%) study subjects were a color identification problem, there was a significant proportion of using smartphones, among all study subject 468(74.17%) study subjects were using the smartphone for watching movies or playing the game and only 163(25.83%) were free from the smartphone. And also, Table 1 shows among the study subject's consumption of majority (62.76%) were Underweight (BMI<18.5), but 41.5% were normal weight (BMI 18.5-24.9).

Table 1. Socio-demographic and background characteristics of the study subjects (n=631).

Characteristics	n	%
Age (years)		
≤ 6	223	35.34
7-9	317	50.24
10-12	85	13.47
12+	6	0.95
Gender		
Male	314	49.76
Female	317	50.24
Father's Occupation		
Farmer	231	36.61
Self-employed	35	5.55
Business	68	10.78
Daily labor	297	47.07
Others	231	36.61
Types of Families		
Nuclear family	189	29.95
Joint family	442	70.05
Able to watching Television closely (<5ft)		
Yes	423	67.04
No	208	32.96
Problem to reading word in the blackboard		
Yes	25	3.96
No	606	96.04
Color identification problem		
Yes	3	0.48
No	628	99.52
Have any problem with headache		
Yes	197	31.22
No	434	68.78
Have any problem with vomiting		
Yes	59	9.35
No	572	90.65
Have any problem to squint eye		
Yes	7	1.11
No	624	98.89
Used smartphone long time (>4 hours) for playing games or enjoying movies		
Yes	468	74.17
No	163	25.83
Played games in outdoor long time (>4 hours)		
Yes	345	54.68
No	286	45.32
Participant's Body Mass Index (BMI)		
Underweight (BMI<18.5)	396	62.76
Normal weight (BMI 18.5-24.9)	235	37.24
Age		
Mean ± SD	7.4 ± 3	

Prevalence of refractive error among the study subjects

The Figure 1 shows that among the study, subjects present the refractive error 16.0% and the rest 84.0% were a normal vision (Figure 1).

Distribution of refractive error by demographic characteristics (n=631)

Refractive error was significantly higher for females than the male

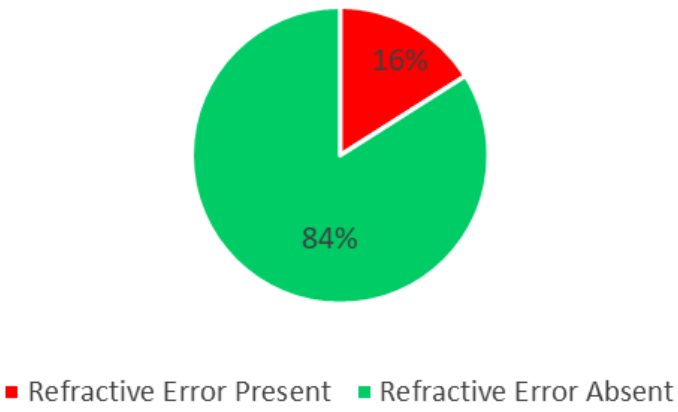

Figure 1. Prevalence of refractive error among the participants (n=631).

Table 2. Distribution of refractive error by demographic characteristics (n=631).

Characteristics	Refractive error		Chi-Square(df)	
	Present (%)	Absent (%)		
Age				
≤ 6	31(13.90)	192(86.10)	1.78(3)	0.6187^{ns}
7-9	52(16.40)	265(83.60)		
10-12	17(20.00)	68(80.00)		
12+	1(16.67)	5(83.33)		
Gender				
Male	38(11.84)	283(88.16)	8.44(1)	0.0037*
Female	63(20.32)	247(79.68)		
Types of Families				
Nuclear family	13(18.06)	59(81.94)	0.25(1)	0.6144^{ns}
Joint family	88(15.74)	471(84.26)		
Father's Occupation				
Farmer	23(15.23)	128(84.77)	3.58(4)	0.4653^{ns}
Self-employed	8(17.39)	38(82.61)		
Business	17(2.94)	561(97.06)		
Daily labor	47(14.83)	270(85.17)		
Others	6(13.33)	39(86.67)		
Participant's Body Mass Index (BMI)				
Underweight (BMI <18.5)	69(17.42)	327(82.58)	1.59(1)	0.20732^{ns}
Normal weight (BMI 18.5-24.9)	32(31.68)	203(86.38)		
Used smartphone long time (>4 hours) for playing games or enjoying movies)				
Yes	73(18.96)	312(81.04)	6.41(1)	0.0113*
No	28(11.38)	218(88.62)		
Have any problem with headache				
Yes	76(38.58)	121(61.42)	108.54(1)	0. 0001***
No	25(5.76)	409(94.24)		
Have any problem with vomiting				
Yes	24(40.68)	35(59.32)	29.46(1)	0. 0001***
No	77(13.46)	495(86.54)		

NOTE. Level of significance: *** for P<0.001, ** for P<0.01, * for P<0.05, ns for not significant.

Table 3. Factors for refractive error among school going children (n=631).

Factors	Unadjusted OR	CI (95%)		P value	Adjusted OR	CI (95%)		P value
		Lower	Upper			Lower	Upper	
Gender								
Male	7.284	3.095	17.141	0	4.776	1.508	15.127	0.008**
Female	Reference	--	--	--	Reference	--	--	--
Used smartphone long time (>4 hours) for playing games /enjoying movies								
Yes	4.21	1.216	9.212	0.048	4.52	1.31	10.217	0.049**
No	Reference	--	--	--	Reference	--	--	--
Have any problem with headache								
Yes	15.49	6.113	39.249	0	11.004	3.211	37.707	0.000***
No	Reference	--	--	--	Reference	--	--	--
Have any problem with vomiting								
Yes	7.532	1.016	55.802	0.04	9.825	1.13	85.367	0.038**
No	Reference	--	--	--	Reference	--	--	--

NOTE. Level of significance: *** for P < 0.001, ** for P < 0.01, * for P < 0.05, ns for not significant.

student (20.32%, p<0.05). Study subjects who used long-duration smartphones (>4 hours) for playing games or enjoying movies had a higher prevalence of refractive error (18.96%, p<0.05). Problem with headache students had a significantly higher prevalence of refractive error than the student who was free from headache (38.58%, p<0.001). Also, the student who had the vomiting problem higher prevalence of refractive error than the student who was free from vomiting (40.68%, p<0.001) (Table 2).

Risk factor for refractive error among school going children

To identify factors that affected the prevalence of refractive error among school-going children, a binomial logistic regression analysis was used. The dependent variable was refractive error status; independent variable including gender, smartphone using a status for playing games or enjoying movies, the problem with headache status, the status of vomiting problem.

Results show that female students (OR=7.284, p<0.05) had a higher likelihood of having refractive error than male children. The likelihood of refractive error 4.5 times higher among the children who used smartphones long time (>4 hours) for playing games /enjoying movies (OR=4.52, p< 0.05). Children who were faces problem with headache (OR=11.004, p<0.01) had more than 11 times higher risk of having refractive error than who were. The chance of having refractive error was associated with the problem with vomiting (OR=9.825, p<0.05) (Table 3).

Discussion

The main objective of this study was to determine the prevalence of refractive errors as well as find out the factors which are associated with the refractive errors, among the school-going children (age 04 years to 15 years) in the rural area. In the present study, the prevalence of refractive error was found at 16% and the criteria for legal blindness was 6/60 as recommended by Md. A. Kader that study was conducted for finding the refractive errors on School going children in north west zone of Bangladesh [10]. In their study result, they found the overall prevalence of refractive error was 9.20%.The prevalence of refractive error in Malaysia is lower 13.4% but in Singapur is higher 36.3% is comparable with this study [11]. In Uganda it was 11.6 % which corresponds to the present study, the exact cause was not mentioned, it might be due to limitation of representativeness [12]. Regarding the refractive error could be compared with Nepal 2.2% and rural India 2.8% that is recent. Is also agreement with Nepal study was an ocular refractive error in the prevalence of refractive error ocular morbidity in school children in Kathmandu 11% [13].

The prevalence of refractive error was scientifically higher with female than male. In table 3. refractive error 4.5 times higher among the children who used smartphones long time (>4 hours) for playing games /enjoying movies. Children have headache, vomiting problem, higher chance to be having refractive error. In Egypt, the prevalence of refractive error was 22.1 and this amount rising due to socio-economical conditions like age, gender, and positive family history. Most important is that the complexity of refractive error is easily preventable and treatable if diagnosis and treatment was be done in proper time.

Conclusion

The refractive error is the major health concern in our country of school-going children in our country but most of the guardians and students are not conscious such this major problem. Parents of the student should be taken consulted with an ophthalmologist for children who complained about any eye problem and the refractive error knowledge should be incorporated in the primary eye care program. In this context, leaflets, posters, radio, television, and newspapers may play an essential role in increasing the student's, teacher, and parents' consciousness. As the study was done among the children of the rural areas and the urban areas was not covered, so to find out the real complete picture for the refractive error among rural and urban areas further study is needed. But it could be concluded that the refractive error is one of the most common causes of visual impairment and has a relationship with female sex, smartphone using time, the problem with headache, and the problem with vomiting, but no association was found with age, family's types, father's occupation, participant's body mass index (BMI) and other risk factors. The majority of students were never examined for visual acuity. So, it could be recommended that children should be examined at the time of entering school and when they are leaving, at least twice during their study period.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Dandona L and Rakhi D. "What is the global burden of visual impairment?." *BMC med.* 4.1 (2006): 1-10.
2. Pizzarello L. et al. "VISION 2020: The Right to Sight: a global initiative to eliminate avoidable blindness." *Arch. ophthalmol*. 122.4 (2004): 615-620.
3. World Health Organization. "Global Initiative for the Elimination of Avoidable Blindness: action plan 2006-2011." (2007).
4. Alam H, et al. "Prevalence of refractive error in school children of Karachi." *JPMA. J. Pak. Med. Assoc*. 58.6 (2008): 322.
5. Wong, T. Y. et al. "The epidemiology of age related eye diseases in Asia." *Br. J. Ophthalmol*. 90.4 (2006): 506-511.
6. Kalikivayi V, et al. "Visual impairment in school children in southern India." *Indian J. ophthalmol*. 45.2 (1997): 129.
7. Murthy, G. V. S., et al. "Refractive error in children in an urban population in New Delhi." *Investig. ophthalmol. vis. sci*. 43.3 (2002): 623-631.
8. World Health Organization. "Preventing blindness in children: report of a WHO/IAPB scientific meeting." (2000).
9. Statistics, O. F. "Statistical Pocketbook Bangladesh, 2015." *Bangladesh Bur. Stat*. (BBS) (2002).
10. Kader A, et al. "Study of Refractive Errors on School going Children in North

West Zone of Bangladesh." *TAJ: J. Teach. Assoc.* 29.1 (2016): 1-6.

11. Saw, S, et al. "Ethnicity-specific prevalences of refractive errors vary in Asian children in neighbouring Malaysia and Singapore." *Br. j. ophthalmol.* 90.10 (2006): 1230-1235.
12. Saad, A., and B. M. El Bayoumy. "Environmental risk factors for refractive error among Egyptian schoolchildren." *EMHJ-East. Mediterr. Health J.* 13 (4), 819-828, 2007 (2007). (2007).
13. Nepal, B. P., et al. "Ocular morbidity in schoolchildren in Kathmandu." *Br. J. Ophthalmol* 87.5 (2003): 531-534.

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Influence of Tocilizumab on Respiratory Support Requirements in non ICU COVID-19 Patients

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Abstract

Introduction: Complications in COVID-19 are coupled With Acute Respiratory Distress Syndrome (ARDS) and Cytokine Release Syndrome (CRS). Interrupting IL-6 signaling by tocilizumab may be beneficial in those conditions.

Methods: We conducted retrospective observational study in patients with severe COVID-19 pneumonia receiving tocilizumab plus standard therapy. We compared respiratory support levels at hospitalization, before and after tocilizumab admission.

Results: Ninety-two patients fulfilled Serbian Therapy Protocol criteria and received tocilizumab in two separate doses (8 mg/kg i. v. per dose). Patients receiving conventional oxygen therapy before tocilizumab (max 15 l/min) showed significant decrease in respiratory support (z=-3.200, p=0.001) after the treatment, and lower mortality risk when compared to patients requiring high flow oxygen therapy before tocilizumab treatment (0.36 vs. 1.29).

Conclusion: Our results suggest beneficial effect of tocilizumab in addition to conventional therapy in respiratory support requirements, especially in earlier stages of ARDS and CRS.

Keywords: Tocilizumab • COVID-19 • Respiratory support • Oxygen therapy

Introduction

In December 2019, SARS-CoV2 changed the world we knew and triggered the greatest medical emergency in this century. WHO reports more than 600 million confirmed cases of COVID-19 and over 6 million deaths caused by multiorgan failure related to this virus. Clinical worsening and fatal outcomes are mostly induced by Acute Respiratory Distress Syndrome (ARDS), and cytokine release syndrome (CRS) [1, 2]. Both conditions are coupled with IL-6 signalization, leading to acute-phase proteins production and release, chemotaxis, increased vascular permeability, complement activation followed by intravascular coagulation, and further metabolic dysregulation [3,4]. Considering this, it is likely to understand why IL-6 serum levels correlate to the level of respiratory failure and hypoxia, as some recent studies confirmed [5-7].

For this reason, WHO approved the use of anti-IL-6 receptor monoclonal antibodies (e.g. tocilizumab) for the treatment of severe COVID-19, since they are already accepted as the immunological therapy for rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, systemic sclerosis-associated interstitial lung disease, and CRS [8]. However, the available data about the efficiency in COVID-19 are controversial. While some authors report clinical recovery, lower mortality rate, and need for mechanical ventilation in groups treated with monoclonal antibodies for IL-6 receptor, the others find no benefits of this treatment [9,10].

Serbian therapy protocol for COVID-19 recommends the use of tocilizumab in clearly defined indications, so we tried to examine whether tocilizumab in addition to standard therapy is capable of attenuating respiratory failure in those patients. We assumed that the use of tocilizumab will be beneficial, lowering the level of respiratory support and the need for mechanical ventilation.

Subjects and Methods

We conducted an observational, retrospective study in patients suffering from severe COVID-19 pneumonia, hospitalized in specialized COVID hospital Krusevac, University Clinical Center Nis. The primary outcome was the change of respiratory support (lower as a positive outcome, and higher as a negative outcome). Secondary outcomes were the need for mechanical ventilation, discharge from hospital, or death. The data were collected from 1 January to 1 February 2021. We included only non-ICU patients receiving conventional oxygen support at simple face mask (max 15l/min)- conventional oxygen group –CO group, or High Flow Oxygen Therapy (HFOT) group-HF group, between 18 years and 90 years old, which fulfilled the criteria for tocilizumab treatment described by the 10th Serbian protocol for Covid-19 (positive nasopharyngeal swab for SARS-CoV2, moderate to a severe clinical condition, severe hypoxia requiring oxygenation, ARDS confirmed with RTG or CT, confirmed CRS with an increase of CRP>50 mcg/l coupled with IL-6>40 ng/l). Tocilizumab was administrated in two separate doses, 8 mg/kg i.v. (max. 800 mg) per dose to each patient.

Excluding criteria for our survey were: non-compliance for the criteria above, contraindications for tocilizumab, and patients already hospitalized in ICU.

Ninety-two consecutive patients in total fulfilled criteria and were analyzed. There were 56 (60.9%) men, and 36 (39.1%) women, aged between 37 years and 90 years old. Two more patients have met our criteria for follow-up but were intubated and admitted to ICU before the medicine admission, so were not considered in this paper.

All the patients also received standard therapy for COVID-19 defined by a current therapy protocol at the moment of hospitalization, which considered: oxygenation, antibiotics, vitamins, antiviral drugs (favipiravir), glucocorticoids (dexamethasone or methylprednisolone), and anticoagulants. Tocilizumab and glucocorticoids doses were calculated according to the body weight for each patient. Favipiravir was administrated only in patients with positive nasopharyngeal swab for SARS-CoV2, in less than five days from symptoms onset. Each patient fulfilling these criteria received Favipiravir twice a day for five days, 1600mg per dose for the first day, and 600mg per dose for the rest four days. Vaccines for COVID-19 were not available at that period of time in Serbia, so all the patients were not vaccinated.

Since the mortality caused by COVID-19 was enormous at that time, and Tocilizumab had shown significant beneficial effect, we decided to give the medicine to all the patients meeting criteria. Instead of having Tocilizumab and control group, we designed the study in the following manner: due to lack of a matched control group, we collected day-to-day data of respiratory support level for every patient, and set three-time intervals in order to extract data of respiratory support for each patient individually (T1-hospital admission, T2-directly before tocilizumab administration, and T3 –up to 20 days after administration of the drug). These variables included levels of respiratory support at these three different time periods for each patient. For this purpose, we ranked the level of respiratory support from 0 to 4: 0-no oxygen support, 1-conventional oxygen at simple face mask (CO), 2-high flow oxygen therapy (HF), 3-non-invasive ventilation (NIV-CPAP), and 4- Mechanical Ventilation (MV). Finally, we had three ordinary variables (OV): OV1 - respiratory support level at hospital admission, OV2-respiratory support level before tocilizumab and OV3-respiratory support level after tocilizumab administration.

Respiratory support was determined according to following parameters:

- General condition,
- Arterial blood saturation
- Arterial blood gas analysis (PaO/FiOratio) and
- Chest X-ray/MSCT.

Hemodynamics, saturation, and consciousness were monitored constantly, while samples of arterial blood were analyzed every morning, or more often if necessary. Patients underwent diagnostic imaging every 5 days-7 days, or in case of unexpected worsening. Respiratory support for non-intubated patients remained the same as long as saturation was above 90%, arterial pO_2 above 50 mmHg, arterial pCO_2 under 55 mmHg, consciousness preserved, and chest X-ray without signs of progression.

Escalation from conventional oxygen therapy to high flow oxygen therapy was done when a patient at simple facemask at 10-15L/min, did not achieve the set goal Spo2 above 90%. Criteria for escalation of oxygen therapy from HFOT to NIV or MV was persistent respiratory distress-RR>40 breaths/ min, signs of labored breathing, use of accessory muscles of respiration, copious airway secretions, ABG: metabolic/respiratory acidosis, pH<7.25, PaO_2<55 mmHg, $PaCO_2$>55 mmHg, SpO_2<90% on current oxygen delivery device, signs of hemodynamic instability-MAP<60 mmHg, requirement of inotropic support (norepinephrine>0.10 μgr.kg.min^{-1}) with normal CVP, CRT>10 seconds, lactate ≥ 4.0 mmol/L, neurological impairment (GCS ≤ 8).

Weaning from HFOT may be commenced once the following criteria are met: patient has recovered from the severe acute respiratory distress syndrome (i.e., PaO_2/FiO_2>150), SpO_2>90% on FiO_2 ≤ 0.4, no signs of respiratory distress such as agitation or anxiety, respiratory rate ≤ 25/min, heart rate ≤ 120/min, systolic blood pressure ≥ 90 mmHg, arterial pH ≥ 7.35.

Weaning completely from simple face mask oxygen therapy was done if clinical goal of Spo_2-92% maintained after discontinuation.

Statistical analysis

Data were analyzed in IBM SPSS Statistics. In order to determine descriptive characteristics, we used Mean, Mode, Median, and Standard Deviation (SD). In order to determine the differences between groups, we used non-parametric tests of differences. For predicting treatment outcome we used discharge/death as dichotomous dependent variable for Binary Logistic Regression. In another Binary Logistic Regression, we used clinically improved/clinically got worse after tocilizumab administration as dichotomous dependent variable, while, for the same purpose, we used laboratory parameters (CRP, leukocytes, D-dimer, procalcitonin, AST, ALT, thrombocytes, ferritin, creatinine and IL-6), age, gender, time from symptoms onset to drug administration, and time from hospitalization until drug administration as independent variables.

Results

We enrolled 92 patients in total, aged 37-90, (66.88 ± 11.75, 25% were younger than 59.5 years, and 25% were older than 74.75 years old). Laboratory parameters, gender and age distribution before and after tocilizumab treatment in CO and HF patients are shown in Table 1. Mean time from symptoms onset and hospital admission to tocilizumab administration were 8.7 ± 7.74, and 2.96 ± 5.14 days. Mean follow-up time was 10.67 ± 6.73 days per patient.

In order to determine the effect of tocilizumab on respiratory support modification, we compared mean ranks of respiratory support in three-time intervals mentioned earlier in the paper. A Friedman test indicated that there was a statistically significant increase in respiratory support from hospitalization (Md=2.13) to tocilizumab administration (Md=2.27) and a decrease after the treatment (Md=1.60), χ^2 =31.098, p<0.001. Of sixty patients in CO group, after the treatment 80% of them did not require oxygen therapy, 1.7% remained on the same support level, and 18.3% had to be transferred to higher respiratory support (HF, NIV or MV) until the end of follow-up. A Wilcoxon Signed-Ranks test found a significant decrease in respiratory support level after the treatment (z=-3.20, p=0.001, effect size r=-0.41).

Table 1. Baseline laboratory parameters, gender and age distribution before and after tocilizumab treatment in CO and HF group.

Group		Before tocilizumab treatment		After tocilizumab treatment			
				Clinically improved*		Clinically got worse**	
		Mean	SD	Mean	SD	Mean	SD
CO	N	60		48 (80%)		12 (20%)	
	Gender: M/F	36/24		34/14		2/10	
	Age (Years)	66.68	11.981	66.42	12.079	67.75	12.039
	CRP	145.76	78.565	13.406	26.702	10.283	6.775
	Leukocytes	8.6	3.69	11.595	7.711	20.658	12.623
	D-dimer	2939.137	4579.354	1713.809	2866.458	6092.727	7110.617
	Procalcitonin	0.17	0.057	0.205	0.063	0.206	0.05
	AST	51.929	23.442	54.86	49.663	63.25	59.386
	ALT	51.754	34.101	120.488	100.653	77.166	53.046
	Thrombocytes	225.81	94.288	292.441	97.306	274.666	91.264
	Ferritin	1287.694	1296.363	618.435	486.783	903.383	970.258
	Creatinine	108.807	115.292	83.906	39.136	114.833	106.985
	IL-6	87.546	73.162	136.35	309.516	442.333	410.543
HF	N	32		15 (46.9%)		17 (53.1%)	
	Gender: M/F	20/12		12/3		8/9	
	Age (Years)	67.25	11.481	60.8	10.234	70.29	11.947
	CRP	160.687	104.641	26.446	47.304	35.25	31.57
	Leukocytes	11.14	4.907	11.213	4.325	21.775	16.996
	D-dimer	3372.187	3882.782	2519.333	2326.82	5582.5	5007.135
	Procalcitonin	0.19	0.064	0.209	0.096	0.208	0.068
	AST	62.25	32.497	39.466	20.465	54	26.536
	ALT	83.531	89.361	116	131.528	79.666	79.538
	Thrombocytes	265	97.678	336.666	165.579	288.75	87.037
	Ferritin	1731.217	1376.983	1408.583	1447.448	957.562	686.891
	Creatinine	104.406	85.38	70.8	13.459	139.75	134.632
	IL-6	85.203	74.139	685	304.055	606.125	406.786

*Required lower oxygen support after tocilizumab; for CO group: no oxygenation; for HF group: CO support or no oxygenation.

**Required stronger oxygen support after tocilizumab or support remained the same; for CO group: CO support,HF, NIV or MV support; for HF group: HF, NIV or MV support.

In the HF group counting thirty-two patients,43.8% of patients discontinued oxygen therapy, 3.1% continued oxygen therapy but on conventional O_2, 15.6% remained on HF, and 37.5% required stronger support (NIV and MV) after tocilizumab admission. Although the number of patients obtaining clinical improvement is not negligible, Wilcoxon Signed-Ranks testdid not find a statistically significant difference between respiratory support before and after tocilizumab (z=-0,79, p=0,43). Figures 1 and 2 show distribution of the patients according to respiratory support after tocilizumab administration in CO (Figure 1) and HF group (Figure 2).

A logistic regression was calculated to predict treatment outcome (discharge/death) based on gender, age, time from symptoms onset to drug administration, time from hospitalization until drug administration, CRP, leukocytes count, D-dimer, procalcitonin, AST, ALT, thrombocytes, ferritin, creatinine, and IL-6. The logistic regression model was statistically significant, χ^2 (14, N=92)=33.668, p=0.002. The model explained between 37.4% (Cox & Snell R2) and 50.7% (Nagelkerke R2) of the variance and correctly classified 83.3% of cases. As Table 2 shows, five independent variables were associated with treatment outcome (gender, time from symptoms onset to drug administration, time from hospitalization until drug administration, thrombocytes, and creatinine).

Also, a logistic regression was calculated to predict discontinuation of oxygen therapy based on gender, age, time from symptoms onset to drug administration, time from hospitalization until drug administration, CRP, leukocytes, D-dimer, procalcitonin, AST, ALT, thrombocytes, ferritin, creatinine and IL-6. The logistic regression model was statistically significant, χ^2 (14, N=92)=28.019, p=0.014. The model explained between 32.2% (Cox & Snell R2) and 44.5% (Nagelkerke R2) of the variance and correctly classified 81.9% of cases. As Table 3 shows three independent variables were associated with oxygen therapy discontinuation (gender, time from hospitalization until drug administration, and Thrombocytes).

Among all the patients, 19 were admitted to ICU and 14 underwent intubation. Fifty-eight patients were discharged from the hospital, from

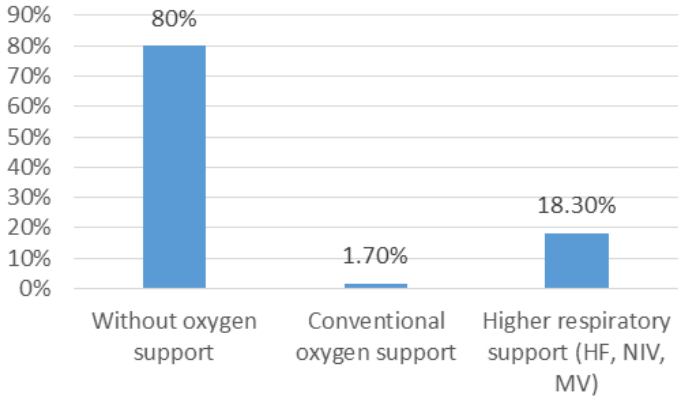

Figure 1. Distribution of patients according to respiratory. support after tocilizumab admission in the CO group.

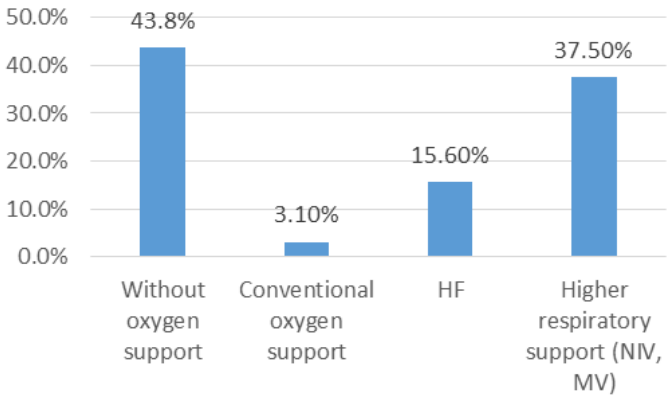

Figure 2. Distribution of patients according to respiratory support after tocilizumab admission in the HF group.

Table 2. Regression coefficients for predicting therapy outcome.

Variable	B	S.E.	Wald	df	p	Exp(B)	95% CI
Gender***	3.057	0.972	9.881	1	0.002**	21.254	[3.161, 142.925]
Age	-0.021	0.037	0.343	1	0.558	0.979	[0.911, 1.051]
Time from symptoms onset to drug administration	0.146	0.07	4.378	1	0.036*	1.158	[1.009, 0.315]
Time from hospitalization until drug administration	-0.579	0.295	3.854	1	0.050*	0.561	[0.315, 0.999]
CRP	0.004	0.004	1.013	1	0.314	1.004	[0.996, 1.012]
Leukocytes	0.148	0.097	2.333	1	0.127	1.159	[0.959, 1.402]
D-dimer	0	0	0.065	1	0.798	1	[1.000, 1.000]
Procalcitonin	17.04	14.022	1.477	1	0.224	25139698.07	[0.000, 2.166E+19]
AST	0.021	0.017	1.491	1	0.222	1.021	[0.988, 1.055]
ALT	-0.002	0.006	0.097	1	0.755	0.998	[0.986, 1.010]
Thrombocytes	-0.018	0.008	4.337	1	0.037*	0.983	[0.966, 0.999]
Ferritin	0	0	0.025	1	0.874	1	[0.999, 1.001]
Creatinine	0.008	0.004	4.382	1	0.036*	1.008	[1.001, 1.016]
IL-6	0.004	0.005	0.672	1	0.412	1.004	[0.994, 1.015]

*p<0.05, **p<0.01; ***values: 0: male, 1: female

Table 3. Regression coefficients for predicting discontinuation of oxygen therapy.

Variable	B	S.E.	Wald	df	p	Exp(B)	95% CI
Gender***	2.698	0.909	8.806	1	0.003**	14.856	[2.500, 88.292]
Age	-0.004	0.035	0.011	1	0.917	0.996	[0.930, 1.068]
Time from symptoms onset to drug administration	0.131	0.068	3.751	1	0.053	1.14	[0.998, 1.302]
Time from hospitalization until drug administration	-0.575	0.284	4.093	1	0.043*	0.563	[0.323, 0.982]
CRP	0.007	0.004	2.767	1	0.096	1.007	[0.999, 1.015]
Leukocytes	0.128	0.092	1.943	1	0.163	1.136	[0.949, 1.360]
D-dimer	0	0	0.052	1	0.819	1	[1.000, 1.000]
Procalcitonin	15.196	13.289	1.308	1	0.253	3978836.5	[0.000, 8.154E+17]
AST	0.029	0.017	2.87	1	0.09	1.029	[0.995, 1.064]
ALT	-0.004	0.006	0.313	1	0.576	0.996	[0.984, 1.009]
Thrombocytes	-0.017	0.008	4.439	1	0.035*	0.983	[0.967, 0.999]
Ferritin	0	0	0.007	1	0.934	1	[0.999, 1.001]
Creatinine	0.002	0.004	0.203	1	0.652	1.002	[0.993, 1.011]
IL-6	-0.002	0.004	0.207	1	0.65	0.998	[0.989, 1.007]

*p<0.05, **p<0.01; ***values: 0: male, 1: female

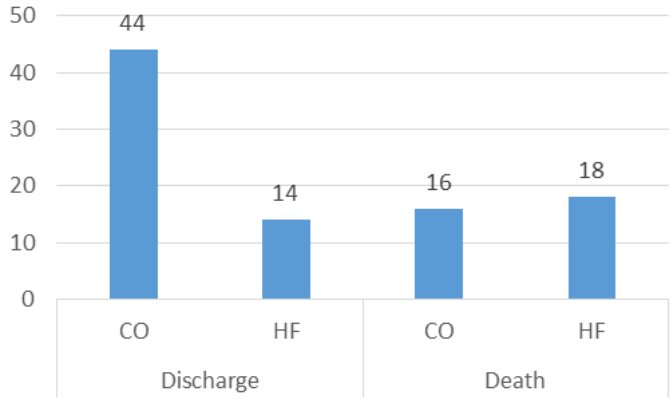

Figure 3. The treatment outcome for CO and HF group.

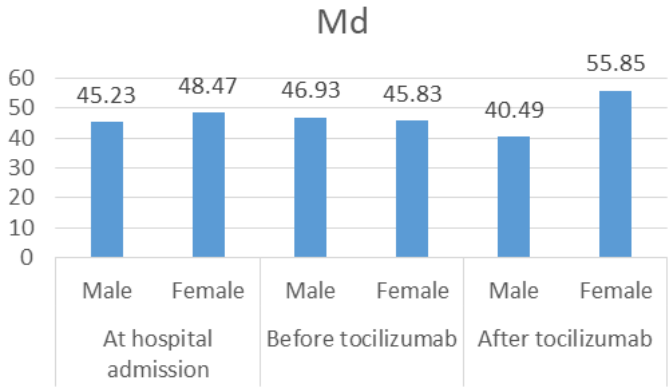

Figure 4. Respiratory support median distribution in male vs. female at hospital admission, before tocilizumab and after tocilizumabadministration.

which 44 patients were receiving CO before tocilizumab administration, while the rest were receiving HF. Among the 34 patients who died, 16 were receiving CO before tocilizumab administration, while 18 were receiving HF. Patients receiving HF before tocilizumab admission had 3.54 times higher mortality risk when compared to patients receiving CO before the treatment (0.36 vs. 1.29) (Figure 3).

Mann-Whitney test did not find significant gender differences in respiratory support distribution at hospital admission (U=937, z=-0.708, p=0.479), or before tocilizumab (U=984, z=-0.233, p=0.816). However, the difference was obtained after the treatment (U=671.5, z=-3.242, p=0.001, effect size r=-0.338) revealing that women needed higher oxygen support than men (Md=55.85, n=36 vs. Md=40.49, n=56). While these gender differences were analyzed separately for three-time intervals (at hospital admission, before tocilizumab and after treatment), the Figure 4 combines these data into one image.

Discussion

SARS-CoV2 enters human cells by Angiotensin-Converting Enzyme (ACE) homolog-2 (ACE2) [11], the receptor that is highly expressed in the lungs [12]. Inflammation coupled with viral infection causes CRS mediated by IL-6 in up to 20% of cases of COVID-19, which is followed by more severe clinical conditions and increased mortality risk [13]. The reaction is also known as "cytokine storm" and is characterized by T-lymphocyte proliferation and enormous IL-6 release [14]. In interaction with IL-6 receptor, this cytokine stimulates acute-phase protein secretion, fever, leukocytosis, increased vascular permeability and hypotension, angiogenesis, intravascular coagulation, and multiple foci of inflammation [4,15-19]. The reaction in the lungs leads to tissue damage, alveolar fluid retention, and respiratory membrane thickening, ending with respiratory failure and hypoxia [20]. Considering pathogenesis, we hypothesized that interrupting IL-6 signalization pathway will significantly mitigate pulmonary damage, shown in the respiratory support demand.

Our results show that tocilizumab administration in group receiving CO support, as the lowest level of respiratory support, significantly improves hypoxia and reduces the need for further oxygenation, with gender and CRP as strongest predictors of discontinuation of oxygen therapy. On the contrary, in the HF group, we did not find a significant improvement. According to this, we concluded that in our patients tocilizumab treatment gave better results when applied in earlier stages of the disease, with less extensive lung damage. Also, we obtained clinical improvement, reduced ICU admission, need for MV, and mortality risk in patients with less severe pneumonia. We cannot exclude the importance of standard therapy, by which all the patients received glucocorticoids and anticoagulant therapy,and some of them antiviral therapy as well. We have also noticed that men in our group had better therapy responses, and a greater survival rate than women, supporting the idea of gender-based differences in the COVID-19 course and outcome.

Klopfenstein et al. received similar results in a retrospective case-control study at the very beginning of the pandemic [21]. They found tocilizumab administration in severe COVID-19 pneumonia to reduce the mortality and MV rate (27% in TCZ group vs. 52% in control group, p 0.009). Later, RECOVERY trial with 4116 patients in total and 2022 receiving tocilizumab, obtained the same (35% vs. 42%, risk ratio 0.84, 95%CI 0.77-0.92, p<0.0001) [22]. The meta-analysis by Snow et al. covering 10 RTC and 6 493 patients, of which 3358 treated with tocilizumab also evaluated the mortality risk and risk for MV [23]. They obtained significantly lower mortality risk in the tocilizumab group (24.4% vs. 29.0%; OR 0.87 (0.74-1.01); p=0.07; I2=10%; TSA adjusted CI 0.66-1.14), but not the risk for ICU admission, as well. Additional meta-regression confirmed the relation between tocilizumab and obtained results, especially in patients with more severe pneumonia.

One of our study limitations is the absence of the control group that would receive a placebo, but we designed the study as nest case control with evaluation of starting data and proportion of patients requiring higher or lower oxygen supply and we intended to compare data at the start and at the end of hospitalization. As we have mentioned earlier, this was the beginning of the second wave which threatened to overcome the previous one in mortality rate; Tocilizumab already showed some beneficial effect and was in the National Covid 19 guide, therefore we decided to give it to all the patients fulfilling criteria, hoping to lower complications and mortality. Further, our patients were mostly elderly people, with 25% older than 75 years old, and having one or more comorbidities which could have impacted on the disease course and therapy response. And finally, we had to use non-parametric tests for statistical analysis owing to distribution. Our study has some advantages, as well. All of the patients received the same standard therapy, following the protocol. We minimized the influence of other variables on the outcome by comparing the respiratory support before and after tocilizumab admission.

Conclusion

To conclude, our results are in concordance with other studies. The addition of tocilizumab to standard therapy in severe COVID-19 pneumonia seems to have a beneficial effect, especially when administrated in earlier stages of respiratory failure. More RTCs and meta-analyses are needed in order to form a definite opinion, but the results so far are encouraging.

References

1. Pasrija R, and Mohammad N. "The deregulated immune reaction and cytokines release storm (CRS) in COVID-19 disease." *Int. Immunopharmacol*. 90 (2021): 107225.
2. Xu Z, et al. "Pathological findings of COVID-19 associated with acute respiratory distress syndrome." *Lancet respir. med*. 8.4 (2020): 420-422.
3. Hirano T. "IL-6 in inflammation, autoimmunity and cancer." *Int. Immunol*. 33.3 (2021): 127-148.
4. Tanaka T, et al. "IL-6 in inflammation, immunity, and disease." *Cold Spring Harb. perspect. biol*. 6.10 (2014): a016295.
5. Farooqi F, et al. "Treatment of severe COVID-19 with tocilizumab mitigates cytokine storm and averts mechanical ventilation during acute respiratory distress: a case report and literature review." *Trop. med. infect. dis*. 5.3 (2020): 112.
6. Higgins V, et al. "COVID-19: from an acute to chronic disease? Potential long-term health consequences." *Crit. rev. clin. lab. sci*. 58.5 (2021): 297-310.
7. Jeronimo C, et al. "Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; Metcovid): a randomized, double-blind, phase IIb, placebo-controlled trial." *Clin. Infect. Dis*. 72.9 (2021): e373-e381.
8. Sheppard M, et al. "Tocilizumab (actemra)." *Hum. vaccines immunother*. 13.9 (2017): 1972-1988.
9. Lan S, et al. "Tocilizumab for severe COVID-19: a systematic review and meta-analysis." *Int. j. antimicrob. agents* 56.3 (2020): 106103.

10. Rocco P, et al. "Early use of nitazoxanide in mild Covid-19 disease: randomised, placebo-controlled trial." *Eur. Respir. J*. 58.1 (2021).

11. Wu F, et al. "Author Correction: A new coronavirus associated with human respiratory disease in China." *Nature* 580.7803 (2020): E7-E7.

12. Islam M, et al. "Lung ultrasound for the diagnosis and management of acute respiratory failure." *Lung* 198.1 (2020): 1-11.

13. Moore B. "Síndrome de liberação de citocina em COVID-19 grave." *Science* 368.1 (2020): 473.

14. Morris G, et al. "The cytokine storms of COVID-19, H1N1 influenza, CRS and MAS compared. Can one sized treatment fit all?." *Cytokine* 144 (2021): 155593.

15. Singhania G et al. "Continuation of chronic heart failure therapies during heart failure hospitalization-a review." (2019).

16. Cohen T, et al. "Interleukin 6 Induces the Expression of Vascular Endothelial Growth Factor." *J. Biol. Chem*. 271.2 (1996): 736-741.

17. Stouthard J, et al. "Interleukin-6 stimulates coagulation, not fibrinolysis, in humans." *Thromb. haemost*. 76.11 (1996): 738-742.

18. Merad M, and Jerome C. "Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages." *Nat. rev. immunol*. 20.6 (2020): 355-362.

19. Ranucci M, et al. "The procoagulant pattern of patients with COVID19 acute respiratory distress syndrome." Journal of *Thromb. Haemost*. 18.7 (2020): 1747-1751.

20. Liu B, et al. "Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)?." *J. autoimmun*. 111 (2020): 102452.

21. Klopfenstein T, et al. "Impact of tocilizumab on mortality and/or invasive mechanical ventilation requirement in a cohort of 206 COVID-19 patients." *Int. J. Infect. Dis*. 99 (2020): 491-495.

22. Recovery Collaborative Group. "Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial." *Lancet* 397.10285 (2021): 1637-1645.

23. Snow T, et al. "Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials." *Intensive care med*. 47.6 (2021): 641-652.

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