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MINIREVIEWS

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MINIREVIEWS

Concise review of radiosurgery for contemporary management of pilocytic astrocytomas in children and adults

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Abstract

Pilocytic astrocytoma (PA) may be seen in both adults and children as a distinct histologic and biologic subset of low-grade glioma. Surgery is the principal treatment for the management of PAs; however, selected patients may benefit from irradiation particularly in the setting of inoperability, incomplete resection, or recurrent disease. While conventionally fractionated radiation therapy has been traditionally utilized for radiotherapeutic management, stereotactic irradiation strategies have been introduced more recently to improve the toxicity profile of radiation delivery without compromising tumor control. PAs may be suitable for radiosurgical management due to their typical appearance as well circumscribed lesions. Focused and precise targeting of these well-defined lesions under stereotactic immobilization and image guidance may offer great potential for achieving an improved therapeutic ratio by virtue of radiosurgical techniques. Given the high conformality along with steep dose gradients around the target volume allowing for reduced normal tissue exposure, radiosurgery may be considered a viable modality of radiotherapeutic management. Another advantage of radiosurgery may be the completion of therapy in a usually shorter overall treatment time, which may be particularly well suited for children with requirement of anesthesia during irradiation. Several studies have addressed the utility of radiosurgery particularly as an adjuvant or salvage treatment modality for PA. Nevertheless, despite the growing body of evidence supporting the use of radiosurgery, there is need for a high level of evidence to dictate treatment decisions and establish its optimal role in the management of PA. Herein, we provide a concise review of radiosurgery for PA in light of the literature.

Key Words: Pilocytic astrocytoma; Radiosurgery; Stereotactic irradiation; Low-grade glioma; Radiation oncology; Children

Core Tip: Radiosurgery for pilocytic astrocytomas may be utilized as part of initial management, as adjuvant therapy, or for the salvage of recurrences. Radiosurgery offers a convenient procedure by a condensed treatment schedule with rapid recovery. An improved toxicity profile may be achieved through optimal normal tissue sparing. Accurate setup verification under stereotactic immobilization and image guidance may be achieved, and the procedure is convenient with regards to staff and facility workload.

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INTRODUCTION

Gliomas are neuroepithelial tumors arising from supporting glial cells of the central nervous system (CNS). Low-grade glioma (LGG) may be seen in both adults and more commonly in the pediatric population, and constitutes the most frequent CNS malignancy in children, accounting for approximately one-third of pediatric brain tumors[1-3]. Pilocytic astrocytoma (PA), previously referred to as polar spongioblastoma, cystic cerebellar astrocytoma, or juvenile PA (JPA), is a distinct histologic and biologic subset of LGG initially described by Harvey Cushing in 1931[4,5]. The term "pilocytic" has been used due to the microscopic appearance of cells with long, thin bipolar processes resembling hairs[5]. Rosenthal fibers may be typically found on hematoxylin and eosin staining as elongated eosinophilic bundles. PA comprises roughly 25%-30% and 2%-5% of all CNS tumors in children and adults, respectively[6,7]. These tumors are typically classified as World Health Organization (WHO) grade I tumors[8]. The majority of PAs usually portend favorable prognosis with low growth rates; however, a more aggressive clinical course may be observed in adult PAs and pilomyxoid astrocytomas[9,10]. PAs mostly arise in the cerebellum, chiasmatic, and hypothalamic areas; nevertheless, these tumors may also be seen at other locations including the cerebral hemispheres, brainstem, and spinal cord[11]. Surgery is the main modality of management for PA, and gross total resection is intended to achieve tumor eradication[12-14]. Observation has been considered given the relatively favorable prognosis to spare patients from adverse effects of adjuvant therapy; however, failure to achieve optimal surgical tumor removal may result in subsequent recurrences and the prognosis may be affected by age, disease localization, and extent of resection[15-19]. In this context, radiation therapy (RT) may be considered for the management of selected patients with PA. Irradiation has been shown to improve progression-free survival (PFS) for PA; nevertheless, there have been concerns over the utility of RT due to the risk of radiation-induced toxicity[19-25]. Since a significant proportion of patients with PA are children with vulnerability to adverse effects of irradiation, several strategies have been introduced such as reserving RT for salvage treatment for selected patients, decreasing the total delivered doses, and improving the toxicity profile of radiation delivery through focused stereotactic irradiation[23-25].

Herein, we provide a concise review of radiosurgery for the management of PA in light of the literature.

RADIOSURGERY FOR PA

PA comprises a considerable proportion of LGG particularly in the pediatric population. Typically, PAs are well circumscribed WHO grade I tumors with low growth rates and indolent disease course. PAs may present in the form of solid tumors or may include both cystic and solid components. While some patients may have no symptoms until the tumors grow to a substantial size before diagnosis, symptomatic presentation may occur depending on lesion location and association with critical neurovascular structures. The disease course may also be affected by patient age with adult PAs portending a typically poorer prognosis compared to JPA. Surgery is the principal therapy; however, the extent of resection is a critical factor and patients undergoing incomplete surgical removal of the

tumor may suffer from recurrences particularly within the first years of postoperative period[26]. While there is no consensus on radiotherapeutic management, selected patients may benefit from irradiation particularly in the setting of inoperability, incomplete resection, or recurrent disease. Conventionally fractionated RT has been traditionally utilized for radiotherapeutic management. More recently, stereotactic irradiation strategies have been introduced for improving the toxicity profile of radiation delivery without jeopardizing disease control.

Radiosurgery in the forms of stereotactic radiosurgery (SRS), hypofractionated stereotactic RT (HFSRT), and Stereotactic Body RT (SBRT) has been judiciously used for management of several CNS disorders and tumors throughout the human body with promising therapeutic outcomes[27-41]. Unique features of radiosurgical management include focused and precise targeting of well-defined tumors under stereotactic immobilization and image guidance. Also, radiosurgery typically offers a condensed treatment schedule, which may be particularly well suited for children with requirement of anesthesia during irradiation. While conventionally fractionated RT is delivered over 5 to 6 wk, overall treatment time is significantly reduced in radiosurgical management, which includes the delivery of a single or a few fractions in a significantly shorter overall treatment time. Since a substantial proportion of patients with PA are children, the requirement for daily anesthesia is a critical consideration and abbreviated treatment with radiosurgery may offer a viable radiotherapeutic approach. Multiple convergent beams are focused on the target to achieve excellent target coverage in radiosurgical applications. Steep dose gradients around the target allow for optimal normal tissue sparing, which may be of utmost importance for the management of children with PA to improve the toxicity profile of radiation delivery. The need for expanding the target with margins to account for setup uncertainties is eliminated or minimized under image guidance and robust stereotactic immobilization of the patients which may contribute to reduced normal tissue exposure in radiosurgery of PAs. Table 1 shows summarized data from selected series of stereotactic irradiation for management of PA in pediatric and adult patients.

Murphy *et al*[42] assessed outcomes of Gamma Knife stereotactic radiosurgery (GKSRS) for PA. Median patient age was 14 years (range: 2-84 years) at the time of GKSRS. Median tumor volume was 3.45 cc (range: 0.17-33.7 cc). Median margin dose was 14 Gy (range: 4-22.5 Gy). At last follow-up, 5- and 10-year overall survival (OS) rates were 95.7% and 92.5%, respectively, whereas 5- and 10-year PFS rates were 74.0% and 69.7%, respectively. In this largest study of single session GKSRS including 141 patients from 9 International Radiosurgery Research Foundation centers, the authors concluded that GKSRS provided favorable long term PFS and OS[42].

Trifiletti *et al*[43] from the University of Virginia evaluated GK-based stereotactic irradiation in a series of 28 patients with PA. Median age was 17.4 years (range: 2-70.3 years). Median tumor volume was 1.84 cc and the median margin dose was 16 Gy. One patient received multi-fraction SRS with a total dose of 15 Gy delivered in three fractions. Local tumor control rate was 93% without adverse radiation effects. Actuarial PFS rates at 1, 3, 6, and 12 years were 96%, 96%, 96%, and 80%, respectively. Authors concluded that favorable tumor control rates may be achieved by SRS as a viable technique for management of PA in the primary or recurrent disease setting[43].

Simonova *et al*[44] assessed long-term outcomes with GK-based stereotactic irradiation for PA. Their series included 25 pediatric patients with a median age of 13 years (range: 3-17 years). Median target volume was 2.7 cc (range: 0.2-25 cc). The 10-year OS and PFS rates were 96% and 80%, respectively. Patients with a planning target volume of 2.7 cc or less had increased PFS. Authors concluded that radiosurgery offers an alternative treatment modality, providing long term local control for management of small residual or recurrent PAs[44].

Lizarraga *et al*[45] evaluated linear accelerator based stereotactic irradiation for progressive residual PAs in a series of 12 patients. Median age at the start of stereotactic irradiation was 21 years (range: 5-41 years). There were no radiation-induced adverse effects in the follow-up period, and probabilities of long-term PFS and disease-specific survival were 73.3% and 91.7%, respectively[45].

Hallemeier *et al*[46] assessed GKSRS for the management of recurrent or unresectable PA in a series of 18 patients treated at the Mayo Clinic. Median age at GKSRS was 23 years (range: 4-56 years). Median treatment volume for GKSRS was 9.1 cc. Median margin dose was 15 and 16 Gy for patients with and without prior RT, respectively. PFS rates were 65%, 41%, and 17% at 1, 5, and 10 years, respectively, at a median follow-up duration of 8 years. OS rates were 94%, 71%, and 71%, at 1, 5, and 10 years after GKSRS, respectively. The authors concluded that GKSRS may serve as a meaningful therapeutic option for management of recurrent or unresectable PAs in the setting of treatment failure with surgery and/or external beam RT considering the durable local tumor control and low permanent radiation induced morbidity with GKSRS[46].

Kano *et al*[47] evaluated GKSRS for the management of newly diagnosed or recurrent JPAs in a series of 50 pediatric patients with a median age of 10.5 years (range: 4.2-17.9 years). Median margin dose was 14.5 Gy. PFS after GKSRS (including tumor growth and cyst enlargement) was 91.7%, 82.8% and 70.8% at 1, 3 and 5 years, respectively, for the entire series at a median follow-up duration of 55 mo. The authors concluded that response to treatment was better in small volume residual solid JPAs, and GKSRS should be considered when resection is not feasible or in the presence of early recurrence[47].

Table 1 Selected series of stereotactic irradiation for management of pilocytic astrocytoma in pediatric and adult patients

Ref.	Publication year and study period	Histology	Number of patients	Age (yr)	Setting	Treatment	Tumor size	Dose	Prior RT	Follow-up duration	PFS / tumor control
Murphy *et al* [42]	2019 (1990-2016)	PA	141	Median age 14 yr (range: 2-84 yr)	As part of initial management or salvage therapy	GKSRS	Median 3.45 cc	Median margin dose 16 Gy	21 patients	Median 67.3 mo	PFS 74.0% at 5 yr; PFS 69.7% at 10 yr
Trifiletti *et al* [43]	2017 (1990-2015)	PA	28	Median age 17.4 yr (range: 2-70.3 yr)	As part of initial management or salvage therapy	GK-based SRS or SRT	Median 1.84 cc	Median margin dose 16 Gy for single fraction SRS, and 15 Gy delivered in 3 fractions for SRT	4 patients	Median 5.4 yr	PFS 96% at 6 yr; Tumor control 93%
Simonova *et al* [44]	2016 (1992-2002)	PA	25	Median age 13 yr (range: 3-17 yr)	As part of initial management or salvage therapy	GK-based SRS or SRT	Median 2.7 cc	Median margin dose 16 Gy for patients receiving single fraction, median dose 25 Gy delivered in 5 fractions for SRT	2 patients	Median 15 yr	PFS 80% at 10 yr
Lizarraga *et al* [45]	2012 (1995-2010)	PA	12	Median age 21 yr (range: 5-41 yr)	Salvage therapy	LINAC-based SRS or SRT	Median 6.5 cc for SRT; Median 1.69 cc for SRS	Median dose 18.75 Gy for SRS and median dose 50.4 Gy delivered in 28 fractions for SRT	0 patients	Median 37.5 mo	PFS 73.3% at long term
Hallemeier *et al* [46]	2012 (1992-2005)	PA	18	Median age 23 yr (range: 4-56 yr)	As part of initial management or salvage therapy	GKSRS	Median 9.1 cc	Median margin dose 15 Gy	10 patients	Median 8 yr	PFS 41% at 5 yr; Tumor control 75%
Kano *et al*[47]	2009 (1987-2006)	PA	50	Median age 10.5 yr (range: 4.2-17.9 yr)	As part of initial management or salvage therapy	GKSRS	Median 2.1 cc	Median margin dose 14.5 Gy	5 patients	Median 55.5 mo	PFS 70.8% at 5 yr
Kano *et al*[48]	2009 (1994-2006)	PA	14	Median age 32 yr (range: 19-52 yr)	As part of initial management or salvage therapy	GKSRS	Median 4.7 cc	Median margin dose 13.3 Gy	6 patients	Median 36.3 mo	PFS 31.5% at 5 yr
Hadjipanayis *et al*[49]	2002(1987-2000)	PA	37	Median age 14 yr (range: 3-52 yr)	As part of initial management or salvage therapy	GKSRS	Median 3 cc	Median margin dose 15 Gy	9 patients	Median 28 mo after GKSRS	Tumor control 68%
Boëthius *et al* [50]	2002 (1978-1997)	PA	19	Mean age 10.6 yr (range: 2-60 yr)	Adjuvant therapy	GKSRS	Median 2.2 cc	Median margin dose 10 Gy	2 patients	Median radiological follow-up 4.7 yr	Tumor control 94.7%
Somaza *et al* [51]	1996 (1990-1993)	PA	9	Mean age 8.6 yr (range: 4-17 yr)	Adjuvant or salvage therapy	GKSRS	Mean tumor diameter 16 mm	Median margin dose 15 Gy	2 patients	Median 19 mo	Tumor control 100%

GKSRS: Gamma Knife stereotactic radiosurgery; LINAC: Linear accelerator; PA: Pilocytic astrocytoma; PFS: Progression-free survival; SRS: Stereotactic radiosurgery; SRT: Stereotactic radiation therapy.

In another study, Kano *et al*[48] separately assessed GKSRS for the management of PA in adult patients. A total of 14 patients treated using GKSRS between 1994 and 2006 were included. Median age was 32 years (range: 19-52 years). Median margin dose was 13.3 Gy, and median radiosurgery target volume was 4.7 cc. At a median follow-up duration of 36.3 mo, 3 patients died and 11 patients were

alive with OS rates of 100%, 88.9%, and 88.9% at 1, 3, and 5 years, respectively, for the entire series. The authors emphasized that PA could behave more aggressively in adult patients, and thus additional treatment strategies could be considered for unresectable PAs located in critical brain areas. The authors concluded that GKSRS was most valuable for patients after maximal feasible surgical resection and delayed cyst progression contributed to late loss of tumor control[48].

Hadjipanayis *et al*[49] performed a retrospective analysis of 37 patients receiving GKSRS at the University of Pittsburgh Medical Center for recurrent or critically located PAs. Median age at GKSRS was 14 years. At a median follow-up duration of 28 mo after GKSRS and 59 mo after diagnosis, 33 (89%) of 37 patients were alive, providing a 7-year actuarial survival rate of 76%. Follow-up imaging revealed tumor control in 25 (68%) of 37 patients. While 10 patients had complete resolution of tumor, 8 had greater than 50% reduction in tumor volume. There were no procedure-related permanent morbidity or mortality. The authors concluded that GKSRS could be used as part of multimodal management for progressive, recurrent, or unresectable PAs and GKSRS could replace fractionated RT and chemotherapy in selected patients as a safe and promising treatment modality[49].

Boëthius *et al*[50] evaluated outcomes of 19 patients receiving GKSRS for PA. Mean age was 10.6 years, and the study group included 16 pediatric patients. Median tumor volume was 2.2 cc. A median marginal dose of 10 Gy was used given that majority of tumors were localized within or in close neighborhood of the brainstem. A satisfactory tumor control rate of 94.7% was achieved at a median radiological follow-up duration of 4.7 years and median clinical follow-up duration of 7 years albeit with a relatively lower GKSRS dose[50].

Somaza *et al*[51] from Pittsburgh University assessed the utility of GKSRS in adjuvant treatment of 9 pediatric patients with growing and unresectable deeply seated PAs. Mean margin dose was 15 Gy. At a mean follow-up duration of 19 mo, tumor control was achieved in all patients with significant tumor shrinkage in 5 patients and no further growth in 4 patients. No patients had early or late toxicity. The authors concluded that GKSRS served as a safe and effective therapeutic modality for management of deeply seated and small volume PAs[51].

Overall, stereotactic irradiation has been utilized for management of PA in both children and adults as a promising treatment modality. Since adverse effects of irradiation constitute major concerns over the use of RT for treatment of PAs, improving the toxicity profile of radiation delivery is a critical aspect of contemporary patient management in the millennium era. Within this context, focused and precise targeting of well circumscribed PAs under stereotactic immobilization and image guidance may offer great potential for achieving an improved therapeutic ratio by virtue of radiosurgical techniques. Another advantage of radiosurgery may be the completion of therapy in a usually shorter overall treatment time, which may be particularly well suited for children with requirement of anesthesia during irradiation. Although radiosurgery is a relatively newer treatment paradigm compared to conventional RT, it has gained widespread popularity and adoption with growing body of evidence supporting its utility. Nevertheless, there is still room for further improvements with the need for high level of evidence to reach multidisciplinary consensus for optimal management of PAs.

CONCLUSION

PA may be seen in both adults and children as a distinct histologic and biologic subset of LGG. Surgery is the principal treatment for management of PAs, however, selected patients may benefit from irradiation particularly in the setting of inoperability, incomplete resection, or recurrent disease. While conventionally fractionated RT has been traditionally utilized for radiotherapeutic management, stereotactic irradiation strategies have been introduced more recently to improve the toxicity profile of radiation delivery without compromising tumor control. PAs may be suitable for radiosurgical management due to their typical appearance as well circumscribed lesions. Focused and precise targeting of these well-defined lesions under stereotactic immobilization and image guidance may offer great potential for achieving an improved therapeutic ratio by virtue of radiosurgical techniques. Given the high conformality along with steep dose gradients around the target volume allowing for reduced normal tissue exposure, radiosurgery may be considered as a viable modality of radiotherapeutic management. Another advantage of radiosurgery may be the completion of therapy in a usually shorter overall treatment time, which may be particularly well suited for children with requirement of anesthesia during irradiation.

Although radiosurgery has a shorter history compared to conventional RT, there is accumulating data on its utility for management of several tumors throughout the human body. In the context of PAs, several studies have addressed its use particularly as an adjuvant or salvage treatment modality. Nevertheless, despite the growing body of evidence supporting the utility of radiosurgery, there is need for high level of evidence to dictate treatment decisions and establish its optimal role in management of PA. We believe that both SRS and SRT may be considered as viable radiosurgical methods for management of PA and selection between SRS and SRT should be based on patient, tumor, and treatment characteristics.

In the context of future perspectives, immunotherapy, identification of driver alterations and introduction of efficacious targeted therapies may pave the way for contemporary treatment approaches for PAs. Further extensive investigation is warranted to develop safe and effective treatment strategies for management of PAs.

FOOTNOTES

Author contributions: Sager O, Dincoglan F, Demiral S, Uysal B, Gamsiz H, Gumustepe E, Ozcan F, Colak O, Gursoy AT, Dursun CU, Tugcu AO, Dogru GD, and Arslan R played significant roles in data acquisition, interpretation of data, and reviewing and writing of the manuscript; Elcim Y, Gundem E, and Dirican B revised the manuscript for important intellectual content; Beyzadeoglu M took part in designing, reviewing, and writing the manuscript and revising the manuscript for important intellectual content; All authors have read and approved the final manuscript.

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MINIREVIEWS

Use of hydroxychloroquine and azithromycin combination to treat the COVID-19 infection

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Abstract

Coronavirus disease 2019 (COVID-19) infection is unequivocally the worst crisis in recent decades, which is caused by a severe acute respiratory virus 2. Currently, there is no effective therapy for the COVID-19 infection. Different countries have different guidelines for treating COVID-19 in the absence of an approved therapy for COVID-19. Therefore, there is an imminent need to identify effective treatments, and several clinical trials have been conducted worldwide. Both hydroxychloroquine [HCQS], chloroquine, and azithromycin (AZ) have been widely used for management based on *in vitro* studies favoring antiviral effects against the COVID-19 virus. However, there is evidence both in favor and against the use of hydroxychloroquine and azithromycin (HCQS+AZ) combination therapy to manage the COVID-19 infection. The combination of hydroxychloroquine and azithromycin was significantly associated with increased adverse events. However, the inference of these findings was from observational studies. Therefore, large randomized trials are imperative to show the future path for the use of HCQS+AZ combination therapy. However, owing to the ban on HCQS use in COVID-19, this may no longer be essential. This review is on the pharmacology, trials, regimens, and side effects of hydroxychloroquine and azithromycin combination therapy.

Key Words: Hydroxychloroquine; Azithromycin; Antiviral effects; QT interval; Randomized controlled trial

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic has raged across the globe imposing a huge burden on the health systems. In absence of definitive treatment or vaccines, many drugs with antiviral properties were repurposed for use against COVID-19 infection. Based on the results of preliminary success in observational studies, Hydroxychloroquine (HCQS) and azithromycin were used extensively in the initial part of pandemic in he management of COVID-19 pandemic. Subsequently, reports of QT prolongation emerged with HCQS and its combination therapy with azithromycin. Later on HCQS was discontinued by major guidelines including World Health Organization. The review traces the emergence and downfall of the combination therapy in management of COVID-19.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is possibly one of the most severe we all have witnessed in recent decades. The COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) and was initially reported in Wuhan, China in December 2019[1]. Currently, more than 250 million cases have occurred across the world, and a total of approximately 5 million deaths have been reported thus far[2]. Social distancing, infection control measures, frequent hand washing, and wearing a mask are the cornerstone of the COVID-19 prevention and control. Currently, there are no known effective therapies (*e.g.*, antiviral medications and vaccines) for the disease apart from vaccines which have been shown to be effective against prevention of COVID infection.

A lack of effective therapy against COVID-19 has led the clinicians to rethink the use of repurposed drugs as an effective treatment for COVID-19. The first repurposed drug to be used was the antimalarial drug chloroquine. It is an analog of hydroxychloroquine that is used to treat autoimmune diseases such as systemic lupus erythematous and rheumatoid arthritis. These drugs have shown antiviral activity and immune-modulatory effects under *in vivo* conditions[3,4]. However, the use of the above mentioned repurposed drug for COVID-19 is based on the results of a small number of observational studies and non-randomized trials, which have been inconclusive. The combination of hydroxychloroquine with a second-generation macrolide (*e.g.*, azithromycin) has also been used, despite limited evidence for its effectiveness[5]. Different studies have shown that treatment with the hydroxychloroquine and azithromycin combination may have an adverse cardiovascular effect of prolonging the QT interval, which may result in predisposition to ventricular arrhythmias[6,7].

Many therapies have been tried for treating COVID-19; however, there have been no long-term studies on the use of these approaches[8]. This review briefly describes the pharmacology, trials, regimens, and adverse effects of the hydroxychloroquine and azithromycin combination therapy.

Methods

We systematically searched the PubMed and Clinical trials.org databases up to December 25, 2021 using several specific keywords (*i.e.*, "COVID-19", "HCQS and azithromycin", or "SARS-COV-2") and retrieved all articles published in the English language that reported efficacy, safety, clinical outcome, and pharmacology for the hydroxychloroquine and azithromycin combination in patients with COVID-19. We compiled all the data and narrated the past, present, and future of HCQS and azithromycin combination in the context of COVID-19.

HCQS

HCQS is a 4-aminoquinolone that is widely used to treat certain autoimmune diseases and dermatological conditions. HCQS is a less toxic by-product of chloroquine, which had been used to treat COVID-19. It is a more soluble hydroxy-analog of chloroquine, which Hans Andersag first synthesized in 1934 and confirmed by military testing during World War II as a safe anti-malarial drug. HCQS has been successfully used during the 20th century to prevent and treat malaria in endemic areas.

According to *in vitro* studies, HCQS can inhibit virus entry, transmission, and replication[9]. HCQS increases the pH of cellular endosomes, which inhibits viral entry and replication. Another primary mechanism is the glycosylation of the virus surface receptor ACE-2[10]. In addition to the antiviral activity, various actions of HCQS consist of immune modulation, anti-inflammatory properties, regulation of proinflammatory cytokines [*e.g.*, tumor necrosis factors, interleukin (IL) 1 and 6], and additional antioxidant activities. Currently, there are irrefutable data on cytokine storm in severe cases of COVID-19, which also affects the prognosis of disease[11]. In such cases, the immunomodulatory effect of HCQS can be used for mechanical benefit. HCQS is a less expensive and readily available drug.

Azithromycin

Azithromycin (AZ) (azithromycin dehydrate) is a macrolide; it is an azalide congener of erythromycin and has shown activity against the Zika virus[12-14]. Azithromycin has an expanded spectrum, better tolerability, and superior drug interaction profile. It is more active against gram-negative bacilli H. influenzae. Its pharmacological properties include acid stability, large tissue distribution, rapid oral absorption (from an empty stomach), high attained concentration inside macrophages and fibroblast, and a long terminal half-life > 50 h. It is primarily excreted unchanged in bile, and renal excretion is 10%. There is a molecular similarity between azithromycin and the sugar moiety of ganglioside; a lipid raft ganglioside acts as host attachment cofactor for respiratory viruses. Owing to this similarity, azithromycin interacts with the ganglioside binding domain of the COVID-19 spike protein[15].

An additional advantage may be the prevention of secondary bacterial infection in cytokine-affected alveoli. Macrolide inhibits the CYP-3A4 enzyme with consequent elevation of hydroxychloroquine levels. In vitro studies have shown that the hydroxychloroquine and azithromycin combination has a synergetic effect on SARS-CoV-2-infected cells[15].

HCQS PLUS AZITHROMYCIN CLINICAL DATA

Studies in favor of the combination therapy -the rise of the Roman empire

A study by Gautret *et al*[16] showed that HCQS was efficient in decreasing the viral nasopharyngeal carriage of COVID-19 in most patients in 3-6 days. On day six post-inclusion, 70% of HCQS-treated patients were virologically cured compared to 12.5% in the control group. The six COVID-19 patients received HCQS+AZ combination therapy for five days (to prevent bacterial superinfection). Five out of six patients' viral load cleared on day three, and all six patients (100%) were virologically cured at day six post-inclusion. Four patients had a lower respiratory tract infection (RTI), and the rest were in the upper RTI group. The adverse effects of the combination therapy were not well documented in the study.

A second pilot study by Gautret *et al*[17] was performed on 80 patients, who received 200 mg of HCQS three times a day for ten days and 500 mg of azithromycin on day one, and 250 mg for the rest 2-5 d. The majority (65/80, 81.3%) of patients had a favorable outcome. Only 15% of the patients required oxygen therapy, and three patients were transferred to the intensive care unit (ICU), of whom two improved. Only one 74-year-old patient died.

A study by Chen *et al*[18] initially demonstrated the efficacy of the drug against COVID-19. The use of HCQS resulted in a significant improvement of clinical symptoms, such as fever (2.2 ± 0.4 d) compared to the control group (3.2 ± 1.3 d), cough (2.0 ± 0.2 d *vs* 3.1 ± 1.5 d), and significant radiological improvement.

Million *et al*[19] evaluated 1061 COVID-19 patients treated with the HCQS+AZ combination therapy for three days and eight-day follow-ups. The majority of patients had mild COVID-19 disease at admission. The primary outcome was to check for worsening of the condition and access to the intensive care unit. Only ten patients (0.9%) were transferred to the intensive care unit. In addition, this therapy prevented death; only eight patients (0.75%) died.

Based on various observational and non-randomized studies, HCQS+AZ has been recommended in other guidelines and national consensus statements.

Studies that did not favor the combination therapy - the emperor has been dethroned!

A study by Chen *et al*[20] enrolled 30 COVID-19 patients; 15 patients were treated with 400 mg of HCQS daily for five days, and the remaining 15 patients were in the control group. The study found no significant differences between patients treated with HCQS and the control group in terms of the pharyngeal carriage of viral RNA at day seven. However, the patients also received other antiviral drugs.

Molina *et al*[21] performed a retrospective study of 368 patients with confirmed COVID-19, who were categorized into three groups based on the treatment with hydroxychloroquine alone (n = 97, HCQS), hydroxychloroquine with azithromycin (HCQS+AZ, n = 113), and no HCQS (n = 158) in addition to supportive background management for COVID-19. The two primary outcomes were death and the need for mechanical ventilation. The abovementioned study found no benefit for the use of HCQS either with or without azithromycin. This therapy did not reduce the risk of mechanical ventilation in hospitalized patients. Increased overall mortality was observed in patients treated with HCQS alone.

Lane *et al*[22] found that short-term HCQS treatment is safe, but adding azithromycin may potentially produce heart failure and arrhythmia owing to the synergistic effect on QT interval. The abovementioned study included 956374 and 310,350 users of hydroxychloroquine and sulfasalazine as well as 323122 and 351956 users of hydroxychloroquine-azithromycin and hydroxychloroquine-amoxicillin, respectively. No excess risk of severe adverse effects was identified when 30-d hydroxychloroquine and sulfasalazine use was compared. However, long-term hydroxychloroquine usage was linked to a higher risk of cardiovascular death (HR 1.65) ,when azithromycin was added to hydroxychloroquine, an increased risk of 30-d cardiovascular mortality, chest pain/angina, heart failure, and a two-fold risk of

cardiovascular mortality in the first month of treatment were observed(HR 2.19).

Rosenberg *et al*[23] conducted a retrospective multicenter cohort study of patients from a random sample of all admitted patients with laboratory-confirmed COVID-19 in 25 hospitals. Among 1438 hospitalized patients with a COVID-19 diagnosis, the probability of death for patients receiving hydroxychloroquine and azithromycin was (25.7%), hydroxychloroquine alone, (19.9%), azithromycin alone (10.0%), and neither drug (12.7%). In logistic models, compared to patients receiving neither drug, cardiac arrest was significantly more likely in patients receiving hydroxychloroquine and azithromycin but not hydroxychloroquine alone or azithromycin alone.

Chorin *et al*[24] found that in COVID-19 patients treated with HCQS+AZ, the corrected QTc interval was significantly prolonged. This discrepancy suggests that QT prolongation may be influenced by patient attributes such as co-morbidities and disease severity.

Mercuro *et al*[25] published data on 90 hospitalized COVID patients in Boston. Corrected QT (QTc) was measured before and after HCQS administration (dosage after day 1: 400 mg/d); 53 received concomitant AZ (dosage not given). The baseline median QTc was longer than average (HCQS-alone group: 472 ms; HCQS+AZ group: 442 ms). Seven patients (19%) receiving HCQS alone developed QTc ≥ 500 ms, a generally agreed-upon measure to discontinue QT-prolonging drugs. For patients on combination treatment, 21% developed QTc ≥ 500 ms.

Bessière *et al*[26] reported on 40 French patients in an intensive care unit who were administered HCQS (400 mg/d for ten days) either alone (45%) or combined with AZ (250 mg/d for five days; 55%). Baseline QTc was not prolonged in this cohort (median: 414 ms). Q ≥ 500 ms was observed in 5% of those receiving HCQS alone and 33% of those receiving both medications. No arrhythmias were observed.

A recently published meta-analysis also showed that the HCQS and AZ combination therapy increased mortality (RR = 1.27; 95%CI 1.04-1.54, *n* = 7 studies)[27].

A solidarity trial included 11330 patients; five arms of 2750 received remdesivir, 954 HCQS, 1411 lopinavir, 2063 interferon, and 4088 no drug. There was no mortality benefit observed in any drug group[28]. Magagnoli *et al*[29] study retrospectively evaluated 804 patients and found no significant reduction in mortality and need for mechanical ventilation with hydroxychloroquine with or without Azithromycin (Table 1).

SIDE EFFECTS OF THE COMBINATION THERAPY

HCQS can cause QT prolongation and increases the risk of polymorphic ventricular arrhythmia, *Torsades de pointes* (TdP), in susceptible individuals. However, this side effect is uncommon; however, other drugs (*e.g.*, azithromycin) can aggravate this risk. Many other drugs (*e.g.*, quinolones and antihistamines) are frequently used, which adds to the risk[30]. It is advised to have baseline ECG to estimate QT interval using Bazett's formula. Those with baseline QTc > 500 ms should have a clinical evaluation if they have risk factors, and the use of HCQS should be preferably avoided (Figure 1). Some clinical factors and QTc interval that predisposes an individual to HCQS toxicity should be evaluated [31] (Figure 2).

Different studies reported that the rate of QT prolongation varied between 10% and 20%. Thus, the addition of AZ to HCQS increased the risk of QTc prolongation. Chorin *et al*[24] found that 11% of patient had QTc > 500 with the combination, while 30% had QTc increase of > 60 ms. Expectedly, some precautions are needed when using both HCQS and drugs, which requires regular monitoring of hematological parameters (RBC, WBC, and platelet count), serum electrolyte levels, blood glucose level owing to the hypoglycemic potential of HCQS and its hepatic and renal functions. The safety of these drugs can be maintained by close monitoring. A risk score by Tisdale *et al*[32] has been used to predict drug-induced QT prolongation (Table 2).

ROLE OF HYDROXYCHLOROQUINE AND AZITHROMYCIN COMBINATION IN HIGH-RISK PATIENTS

COVID-19 is a systemic disorder with a widespread inflammation and hypercoagulable state. During the COVID-19 pandemic, D-dimer has been identified as one of the most common and rapidly detected laboratory results related to coagulopathy. Higher mean blood D-dimer levels have been associated with increased in-hospital mortality in hospitalized patients due to COVID-19. According to a previous study, the ideal mean D-dimer cut-off value for predicting in-hospital mortality was 779 g/L, with 77% sensitivity and 83% specificity (AUC 0.87; 95%CI 0.81-0.94; *P* = 0.001)[33]. Fibrinogen, which is also known as one of the acute phase proteins, is produced in large amounts by the liver in response to IL-1- and IL-6-derived stimulation and is implicated in fibrin production as the final step of a triggered coagulation activity. The fibrinogen levels and degradation products of D-dimer [FSE1] were higher in critical COVID-19 patients compared to those in mild or moderate cases. The values were also higher in

Table 1 Different studies on the use of the hydroxychloroquine and azithromycin combination to treat coronavirus disease 2019 infection

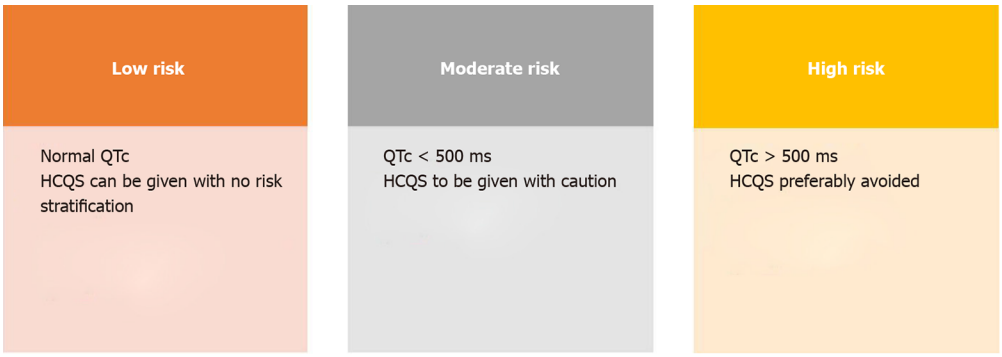
Ref.	Study type	Treatment/duration	Primary endpoint	Outcome	Adverse effects
Gautret *et al*[16]	Open level non-randomized trial	A total of 36 patients; *n* = 14 on HCQS 200 mg TDS; *n* = 6 on HCQS+AZ; *n* = 16 in the control group	Virological clearance at day 6 post-inclusion	Virological clearance at day 6 post-inclusion in the HCQS group (57%), HCQS+AZ (100%), and in the control group (12%)	Not reported well
Gautret *et al*[17]	A pilot observational study (*n* = 80)	Hydroxychloroquine (200 mg every 8 h) for 10 d and azithromycin (500 mg on day 1, 250 mg on days 2-5)	Disease progression: need for oxygen or ICU admission	Viral load decreased over time	Not reported well
Chen *et al* [18]	Prospective open-label, non-randomized trial (*n* = 62)	Patients (31) were assigned to receive (400 mg/d) treatment for five days	Changes in the TTCR of the patients (fever and cough). The appearance of severe adverse reactions was the observation endpoint	A significant response in temperature, cough, and pneumonia was observed in the HCQS group	A total of 4 patients out of 62 had severe illness in the control group, and 2 patients had mild illness in the HCQS group
Chen *et al* [20]	Pilot Study; *n* = 30 treatment-naive patients with confirmed COVID -19	HCQS group (*n* = 15); HCQS 400 mg per day for 5 d plus conventional treatments Control (*n* = 15). Conventional treatment alone	Negative conversion rate of COVID-19 nucleic acid in respiratory-pharyngeal swab on days 7 after randomization	On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the HCQS group and in 14 (93.3%) cases in the control group	A total of 4 cases (26.7%) from the HCQS group and 3 cases (20%) from the control group had transient diarrhea and abnormal LFT
Lane *et al* [22]	Cohort and self-control case series	323, 122 hydroxy-chloroquine plus azithromycin	Severe adverse events, hospital-based events, gastro-intestinal bleeding, acute renal failure, acute pancreatitis, myocardial infarction, stroke, transient ischemic attack, and cardio-vascular events	Azithromycin plus HCQS increased risk of 30-d cardiovascular mortality	
Magagnoli *et al*[29]	Retrospective analysis; (HCQS = 97; HCQS+AZ = 113; Neither = 158)	Dosage and treatment length were not defined	Death, discharge, and ventilation rate	Rates of death in HCQS, HCQS+AZ, and no HCQS groups were 27.8%, 22.1%, and 11.4%, respectively. Rates of ventilation in the HCQS, HCQS+AZ, and no HCQS groups were 13.3%, 6.9%, and 14.1%, respectively	
Rosenberg *et al*[23]	Retrospective multicenter cohort study	1438 hospitalized patients	The primary outcome was in-hospital mortality. Secondary outcomes were cardiac arrest and abnormal electrocar-diogram findings (arrhythmia or QTc prolongation)	HCQS+AZ (25.7%), HCQS alone (19.9%), AZ alone (10.0%), and neither drug (12.7%)	A greater proportion of patients receiving HCQS+AZ experienced cardiac arrest (15.5%) and abnormal ECG findings (27.1%), as did those in the HCQS alone group (13.7% and 27.3, respectively), com- pared with azithromycin alone (6.2% and 16.1%, respectively) and neither drug (6.8% and 14.0%, respectively)
Mercuro *et al*[25]	*n* = 90; Cohort study	HCQS *vs* HCQS+AZ	11% had a QTc increase of > 60 ms; 20% had QTc > 500. The median rise in QTc was higher with combination therapy (23 ms *vs* 5.5 ms). The corres-ponding rates of QTc > 60 ms were also higher with combination arm (3% *vs* 13%) as was the rate of QTc > 500 ms (19% *vs* 21%)	Intractable nausea, premature ventricular complex, right bundle branch block, Torsade's de pointes, hypoglycemia	Combination therapy had greater potential for QT prolongation and arrhythmia
Chorin *at al*[24]	Retrospective COVID -19 patients (*n* = 84)	The patients were on HCQS+AZ	Effect of HCQS/AZ on QTc interval and risk for malignant arrhythmia	Development of ARF was a strong predictor of extreme QTc prolongation	Torsade's de pointes = 0, QTc increase > 40 ms = 30%; QTc > 500 ms = 11%; Significant QTc prolongation in HCQS = 11%
Million *et al*[19]	Non-comparative observational	HCQS+AZ for 3 d	Assess worsening and viral shedding persistence and death	Good clinical outcome and virological cure were obtained in 973 patients	Poor clinical outcome was observed in 46 patients (4.3%); 8 died (0.75%) (74-95

study; n = 1061	within ten days (91.7%)	years old)

HCQS: Hydroxychloroquine; AZ: Azithromycin; COVID-19: Coronavirus disease 2019.

Table 2 Tisdale assessment risk score for drug-associated QTc prolongation. A Tisdale score of < 6 predicts low risk, 7-10 medium risk, and > 11 high risk of drug-associated QT prolongation [Adapted from reference 30]

Risk factors	Points
Age ≥ 68 yrs	1
Female sex	1
Loop diuretic	1
Serum potassium (K^+) ≤ 3.5 MEq/L	2
Admission QTc ≥ 450 ms	2
Acute MI (myocardial infarction)	2
≥ 2 QTc prolonging drugs	3



DOI: 10.5493/wjem.v12.i3.44

Figure 1 Suggested use of hydroxychloroquine therapy according to the baseline QTc interval. HCQS: Hydroxychloroquine.

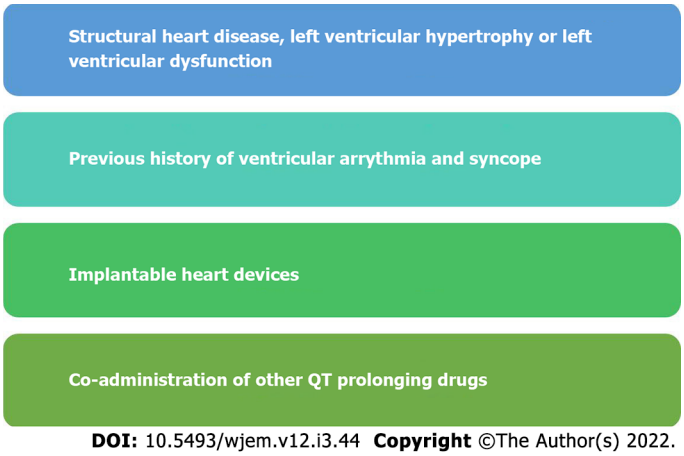


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Figure 2 Risk factors for hydroxychloroquine-induced arrhythmia.

critical COVID-19 patients compared to healthy controls[34].

The overactivation of the immune system, which causes a complement release syndrome, is the key underlying mechanism responsible for the increased coagulation tendency in COVID-19 patients. Increased cytokines, such as IL-6, are a major regulator of the cellular immune response and a trigger for coagulation disorders. Because a hypercoagulable state has been confirmed at both cellular and organ levels, anticoagulant therapy has shown encouraging results in COVID-19 patients[35].

By comparing the data from 101 adult COVID-19 patients hospitalized for mild to moderate ARDS with the data from 92 similar patients, Lamback *et al*[36] found that HCQS in conjunction with azithromycin was ineffective in treating mild to moderate COVID-related ARDS. In the study group, the mean D-dimer value was 758 ng/mL at baseline and peaked at 1193 ng/mL. Fibrinogen levels were also higher in the treatment group compared with the controls. However, enrolling high-risk patients (based on D-dimer and fibrinogen) in combination therapy failed to improve any of the clinical outcomes (*i.e.*, transfer to ICU, death, duration of non-invasive ventilation, and duration of hospitalization).

GUIDELINE RECOMMENDATION

HCQS was an essential part of the treatment regimen in almost all recommendations across the globe. However, it should not be used as a stand-alone therapy in the management of COVID-19 because there is a lack of unequivocal data on effectiveness[30]. The Government of India, Ministry of Health and Family Welfare Guidelines on clinical management of COVID-19 (March 31, 2020) recommended the administration of 400 mg of hydroxychloroquine BD at day one followed by 400 mg OD for the next four days in combination with 500 mg of azithromycin. The revised guideline by the Ministry of Health and Family Welfare on Clinical Management of COVID-19 recommended the administration of 400 mg of hydroxychloroquine (without concomitant AZ) BD at day one followed by 400 mg OD for the next four days[37]. However, the recent iteration of MOHFW before the second wave removed HCQS for use in COVID-19. USFDA also issued a black box warning for its use in COVID-19 infection. After the SOLIDARITY trial, HCQS was removed from the list of essential drugs in COVID-19 disorder[28]. Recently, all major guidelines released have obviated the use of HCQS when treating COVID-19.

LIMITATIONS

Most studies and trials had a small sample size, different drug dosing, duration, varied inclusion criteria, and endpoints, which led to exaggerated study results. In addition, most trials did not include severely ill patients with other organ dysfunction, which may alter drug clearance from the body, leading to toxicity. In addition, non-randomized trials and lack of placebo were areas of concern.

CONCLUSION

Because there is no definitive and promising treatment against COVID-19 and cases are yet to reach the peak, any treatment is better than no treatment. Data from preliminary studies showed that the HCQS+AZ combination was beneficial in virological clearance and was initially used as a possible treatment option for COVID-19. In later studies, combination therapy did not significantly improve, although side effects were higher in the combination arm. Moreover, the combination therapy in hospitalized COVID-19 patients, many of whom may have had concurrent renal or hepatic dysfunction, could have aggravated the QT-prolonging potential of these drugs. This could have led to enhanced morbidity and mortality, which was observed in more recent studies using HCQS combination. In more recent studies, the benefit of using HCQS alone is being questioned, and combination therapy is not warranted. Thus, treating the COVID-19 infection with HCQS, either alone or with AZ, is no longer recommended. Therefore, based on the current evidence, HCQS and its combination with azithromycin are not suitable for the management of COVID-19.

FOOTNOTES

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