Efficacy and Safety of Interferon Alpha-2b in COVID-19: A Systematic Review

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Several drugs have been explored for the antiviral action against COVID-19 disease but none of them has been approved barring few such as Remdesivir which got emergency use authorization from USFDA. Interferon are attractive agents due to their broad anti-viral and immunological properties. Interferon alpha-2b has been recently investigated for this purpose. This study presents a systematic review of all the clinical studies involving Interferon alpha-2b to determine its efficacy and safety. A systematic review of literature was done using relevant terms for 'COVID-19" and "Interferon alpha". The studies evaluating the effect of Interferon alpha were identified and included in the study for qualitative analysis. All four clinical studies have shown that Interferon alpha 2b has efficacy as antiviral agent as shown by different clinical and laboratory parameters. It has also found to be safe and free of any major side effects. Interferon alpha 2b is an effective antiviral agent with potential to be use in COVID-19. This drug has already been given restricted use authorization in India.

Keywords: Antiviral Agents; COVID-19; Interferon alpha.

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) first detected in China in December 2019 soon took the form of pandemic[1,2]. The clinical features of COVID-19 ranges from asymptomatic infection to severe respiratory illness and death[3]. Several therapeutic options have been used for COVID-19 disease. It includes anti-virals such as remdesivir, favipiravir, hydroxychloroquine lopinavir-ritonavir, arbidol and as adjunctive therapy like dexamethasone, tocilizumab and other immunomodulator agents[4]. But, out of which only remdesivir has been approved by regulatory authorities as antiviral drug in several countries including India, US & Japan[5-7]. Other drugs such as favipiravir and ivermectin are being used as off label drugs. In the absence any effective and specific antiviral drug several antivirals are still being evaluated. Recently one more antiviral drug interferon alpha-2b has been approved in India for restricted emergency use[8]. Interferons as a drug are natural choice for SARS-Cov-2 infection owing to its broad-spectrum antiviral activity due to its direct antiviral effect as well as immune response. IFN-alpha has been uses to treat several viral infections chronic hepatitis B, C and recurrent respiratory papillomatosis[9-11]. It has also been used in multiple sclerosis due to their immunomodulatory actions[12]. It has also been shown that SARS-Cov-2 interferes with IFN production and functioning leading to lower level of neutralizing antibodies[13]. IFN-alpha treatment is aimed to reestablish this suppressed immune response and lowering of the virulence

of COVID-19 disease. More specifically the antiviral effect is attributed to binding of IFNs to their receptor on surface of different cells to induce JAKSTAT signaling pathway leading to increased expression of genes responsible for producing antiviral enzyme RNAse I and other chemokines which leads to inhibition of viral replication[14]. The most promising evidence antiviral effect of interferon alpha against SARS-Cov-2 infection comes from its in vitro inhibitory effect which has shown to reduce the virus titer by several thousand times[15]. It led to rapid exploration of this drug in clinical studies as repurposed drug. This study provides the review of clinical studies which has been done to determine the efficacy and safety of IFN-alpha-2b.

MATERIALS AND METHODS

A literature search was performed using terms namely, Interferon alpha 2b or Interferon alfa 2b or Interferon á2b in combination with COVID-19using PUBMED to identify relevant articles. Due to lack of randomized controlled trial non-randomized interventional and observation studies were also included. The flow chart for the selection of relevant article has been shown in Fig.1.

RESULTS

Following are the results of the included studies as shown in table 1.
Pandit A et al.(16)
It was a phase 2 randomized controlled open label study to determine efficacy and safety of single dose of a pegylated interferon alfa-2b (PEG IFN-á2b) with standard of care in adult subjects with moderate COVID-19 admitted in hospital in India. The primary and secondary outcomes were proportion of subjects with improvement in clinical status on WHO scale on day 15 and viral negativity on day 7 &15 respectively. The number of subjects which was randomized in two groups were 20 each. The two groups were comparable at baseline for the demographic characteristics. For primary endpoint 95% of subjects in intervention arm achieved clinical improvement as compared to 68.42% in control arm which was statistically
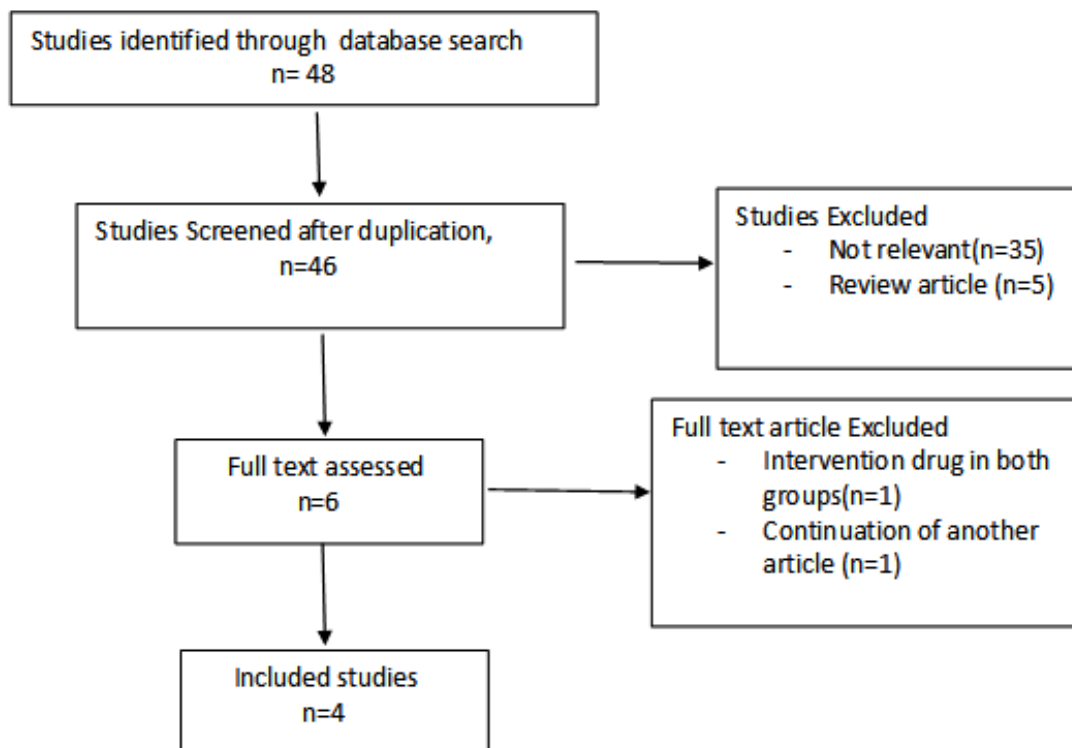

Fig. 1. PRISMA flowchart for selection of included studies

Table 1. General characteristics of the studies included for review

Author, Year	Design	Population	Intervention	Sample size (n1-Inter-vention) n2- Control)	Comparartor	Dosage (IFN α2b)	Outcome measured
Pandit A et al., 2020	Randomized open label study	Adults with lab confirmed COVID-19 infection	PEG IFN α2b+SOC	n1- 20 n2- 20	SOC	Single dose (1μg/kg)	1* improveness in clinical status 2* Viral negativity
Pereda R et al., 2020	Retrospective study	Adults with lab confirmed COVID-19 infection	IFN α2b+SOC	n1- 2165 n2- 130	SOC	3MU(IM) 3times/week for 4 weeks	1* Proportion of patients discharged 2* Case Fatality rate
Wang B et.al., 2020	Retrospective study	Adults with lab confirmed COVID-19 infection	IFN α2b+SOC	n1- 19 n2- 22	SOC	3MU(SC) QOD till viral negagtivity	1* Length of hospitalization 2* Time to viral clearance
Zhou Q et al., 2020	Observational study	Adults with lab confirmed COVID-19 infection	IFN α2b+ARB	n1- 46 n2- 24	ARB	5 mIU twice daily as aerosol by nebulizer	Time to viral Clearance

1*- Primary objective, 2*- Secondary objective SOC- Standard of CareARB- Arbidol

significant. For secondary endpoint of viral negativity similar statistical significant results were observed in favour of intervention. Adverse events were noted in eleven subjects in intervention group and eight subjects in control group. All adverse event were mild in nature.

Pereda R et al.(17)

It was a non-randomized retrospective study on patients who were admitted to the hospital in Cuba with confirmed COVID-19 based on Lab confirmed SAR-Cov-2 positive report. Intervention arm received IFN-á2b along with standard of care which included drugs like lopinavir/ritonavir, chloroquine, azithromycin and oseltamivir while control group received only standard of care. A total of 2165 subjects in intervention arm and 130 subjects in control arm were evaluated for the primary outcome which was proportion of patients discharged from hospital. It was found that 1958 (99%) subjects in intervention group had disease resolution as compared to 64(49.6%) in control group. The odds ratio estimation indicated 56.8 times greater odd to achieve recovery in the intervention group which was highly significant. For the secondary outcome of case fatality rate it was found reduced in intervention group irrespective of the clinical status of the patient. The most common adverse event was diarrhoea and adverse events were mild in nature.

Wang b et al.(18)

It was a single centre retrospective study to evaluate efficacy of the intervention(IFN alpha2b) in terms of length of hospitalization and time to viral clearance in cases with laboratory confirmed COVID-19 infection admitted in hospital in China. A total of 41 patients were evaluated with 19 of them in combination group which received subcutaneous injection of IFN alpha 2b along with oral lopinavir/ritonavir combination. Remaining 22 subjects were in control group and received oral lopinavir/ritonavir only. It was found that the length of hospitalization in combination group was significantly shorter compared to control group (16 ± 9.7 vs 23 ± 10.5 days; P = 0.028). Similarly there was significantly shorter time to viral clearance in combination group compared to control group. There was also no significant difference in adverse event in two group and all adverse events were self-limited.

Zhou Q et al.(19)

It was observational study of adult patients admitted in hospital in China. The treatment was either IFN alone (n=7) or in combination with Arbidol (n= 46)or Arbidol alone (n=24). For the primary enpoint of viral clearance it was found that IFN alone and in combination with Arbidol significantly reduced mean days to viral clearance. Further, IFN therapy also found to reduce CRP and IL-6 levels, both important biomarkers of inflammation. Further study on same patients also found that IFN-á2 treatment led to significantly lower CT scores, compared to treatment with ARB alone[20].

DISCUSSION

Antiviral drugs are important treatment for COVID-19 infections but until now there are no such approved medication with proven efficacy except for remdesivir which has been approved for emergency use authorization in few countries. But the WHO has recommended against the use of remdesivir in hospitalized patients, regardless of disease severity, as there was no evidence that remdesivir is effective in improving survival and other outcomes in these patients[21]. The apparent clinical success of this drug is limited to a few clinical studies.

Most of the drug options come from experience treating SARS, MERS or some other new influenza virus previously. IFNs are cytokines that play a key factor in reducing viral multiplication and modulating host immune response against viral infection. IFNá-2b are being for use in nebulized form or subcutaneous or intramuscular injections and in pegylated form for the management. A phase 2 clinical trial evaluating subcutaneous peginterferon by *Pandit A et al.* was done to evaluate efficacy of IF alpha 2b. The single dose of Pegylated IFN was used. It demonstrated significant improvement in clinical status as well as rapid viral clearance. The phase 3 trial with 250 subjects has also been completed but the results are not yet published. But it has been reported that the efficacy of the drug has been confirmed in this multicenter phase 3 study. On the basis of this report drug controller general of India (DCGI), the regulatory authority for drug approval, has

approved it for restricted emergency use in India.

In one retrospective study by *Pereda R et al.* conducted on hospitalized patients in Cuba, it was reported that IFN alpha is associated with significantly higher proportion of patients getting recovered as well as decreased chances of intensive care requirement. But, the demographic and clinical characteristics of patients at baseline were significantly different. The group which did not receive IFN were having higher comorbidity and also have severe disease. In fact a significant proportion (41%) of those not receiving FN were serious or critical at the time of admission. Because of these unbalance demographic properties and unequal sample size the finding from this study may not be generalized.

Another retrospective study by *Wang b et al.* conducted in China of adult patients admitted in hospital with confirmed COVID-19. The group receiving IFN alpha 2b had significantly shorter duration of hospital stay and time to viral clearance. Though the baseline characteristic of two groups were balance it has small sample size and design of the study is also not robust, it being a retrospective observational study.

Another exploratory study by *Zhou Q et al.,* despite having several limitation such as small and unequal sample size and weak study design suggest some clinical benefit in patients of COVID-19 owing to its antiviral as well as anti-inflammatory effects. Further the aerosol route has the advantage of being simple to administer and specifically target the site of action and lesser side effect.

Limitation

Despite doing exhaustive literature search it is possible to miss few studies either due to unavailability of full text and data or if research is published in language other than english or simply by chance. Further the studies included are not blinded randomized controlled study but either retrospective observational studies except for one open label RCT (Pandit A. et al.) the results from these studies can not be generalized.

CONCLUSION

Above mentioned studies have supported the role of IFN alpha2b in patients of mild to moderate COVID-19, which has shown to shorten time to recovery and viral clearance. A well-designed phase 2 study in India has also confirmed its efficacy and it has already been approved for restricted emergency use in India on basis of finding of phase 3 study which is yet to be published. Further all the studies have found the therapy as safe as none of them reported any severe adverse events. The aerosol route also provides advantage over other drugs owing to easy administration.

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