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OPEN PEER REVIEW

Effects of Interferon β1-a Administration in the First Versus Second Week of Treatment on Recovery in Patients with COVID-19: A Retrospective Study

HamidReza Samimagham, Mehdi Hassani Azad, Mohsen Arabi, Sara Ghazizadeh, Alireza Malektojjari, Golbahar Ghasemi, Mitra KazemiJahromi

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

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1 Original submission

4 comments · 2 Oct 2021 – 27 Nov 2021

Mohammad Kazem Momeni Reviewer

ACCEPT 2 Oct 2021

This review is good practice, has been done well, and can be published without any changes.

Referee 1 Reviewer

REJECT 17 Nov 2021

Dear author/authors
Due to the scientific and grammatical errors in the manuscript entitled “Effect of Interferon in the first week versus the second week of treatment on recovery in patients with COVID-19: A retrospective study”, it is not recommended for acceptance and publication. Some of these errors are listed below:
1- The manuscript should be edited to correct writing and grammatical errors.
2- In the abstract section, the following sentence should be edited: “In severe cases, it affects the surface of immune cells and causes inappropriate responses”.
3- The results part in the abstract section should be edited. It is recommended to delete the following sentences: “The study population included 200 patients who were divided into IFN1 (n=100) and IFN2 (n=100) groups. IFN1 had received beta interferon in the first week and IFN2 in the second week of treatment. The two groups’ baseline demographic data were matched”. This should be mentioned in the materials and methods section.
4- It is suggested that the tests performed in this study be listed in the Methods part of the abstract section.
5- A suitable running title is recommended.
6- All abbreviations used in the manuscript must be written in full when they are used for the first time.
7- In the following sentence: “the body’s natural defense mechanism against this infection is hardly activated”, “hardly activated” is not correct. It should be changed.
8- In the following sentence: “Interestingly, although rapid production of interferon at the onset of the disease is 55 an important factor for increasing lymphocyte T cells, increase interferon in later 56 stages inhibit T cells or deplete lymphoid tissues of them”, “increasing lymphocyte T cells” is not in the correct format.
9- In the following sentence: “ The secondary objective was to investigate the difference between IFN1 and IFN2 groups in terms of WBC (White Blood Cell), Hb (Hemoglobin), Urea, LDH (Lactate dehydrogenase), CPR(C - reactive protein) levels and length of hospitalization”, CPR is not correct. It should be changed to CRP.
10- In the statistical methods section, which test was used to analyze the normal distribution of data?
11- In the results section, the following sentence should be edited: “ In our population 58(58.00%) of patients in 124 the first group and 62(62.00%) of patients in the second group were male”.
12- Table number 1 is not clear. It should be edited.

Associate Editor

MAJOR REVISION 27 Nov 2021

Dear author
reviewer 1:
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12- Table number 1 is not clear. It should be edited.

reviewer 2:
1. The manuscript should be rechecked for language errors.
2. In the Abstract (in the method section), it is not correct to use the expressions IFN1 and IFN2 to indicate the first and second weeks of interferon use.
3. Throughout the article (abstract and …), instead of using the general term interferon, the type of interferon used should be mentioned.
4. In the Abstract (in the results section, lines 23 and 24), INF1 and INF2 should be corrected (IFN) and revised according to objection number 2.
5. In the introduction, the description of the role of interferon in immune responses as well as defense against COVID-19 is inaccurate, and the sources cited in this article have been poorly reviewed.
6. Line 71 does not specify the location and city of the hospital (although it is mentioned later).
7. Lines 75 and 76: What type of interferon did they receive? IFN type 1 (IFNα or IFNβ)? (Although it is mentioned later, in line 80.) Also, grouping patients into IFN1 and IFN2 is incorrect.
8. Information on the use of interferon is incomplete. The type of interferon injection and the day(s) of its injection are not specified. What type of IFNβ is used?
9. Has interferon use been associated with routine treatment?
10. Line 75: What has been the routine treatment?
11. Line 104: CPR is incorrect (CRP).
12. In the results section, percentages should be reported consistently.
13. In the results section, percentages should be reported in the same way (in line 115, 60(60.00%) were male and 40% female).
14. Line 122: Correct the location of the period in “two groups for age and sex. (P-value was 0.12 and 0.17 respectively).”
15. Line 129: INF1 should be corrected.
16. Line 131: (p=0.02) should be corrected to (P=0.02).
17. Modify the phrase INF in the table title.

18. Why is CT scan not mentioned in the study of the effects of interferon?
19. Line 156: (IFN1=15+12, IFN2=24+16,) should be revised.

Editor-in-Chief

MAJOR REVISION 27 Nov 2021

Dear author
reviewer 1:
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4- It is suggested that the tests performed in this study be listed in the Methods part of the abstract section.
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7- In the following sentence: “the body’s natural defense mechanism against this infection is hardly activated”, “hardly activated” is incorrect. It should be changed.
8- In the following sentence: “Interestingly, although rapid production of interferon at the onset of the disease is 55 an important factor for increasing lymphocyte T cells, increase interferon in later 56 stages inhibit T cells or deplete lymphoid tissues of them”, “increasing lymphocyte T cells” is not correctly phrased.
9- In the following sentence: “ The secondary objective was to investigate the difference between IFN1 and IFN2 groups in terms of WBC (White Blood Cell), Hb (Hemoglobin), Urea, LDH (Lactate dehydrogenase), CPR(C - reactive protein) levels and length of hospitalization”, CPR is incorrect. It should be changed to CRP.
10- In the statistical methods section, which test was used to analyze the normal distribution of data?
11- In the results section, the following sentence should be edited: “ In our population 58(58.00%) of patients in 124 the first group and 62(62.00%) of patients in the second group were male”.
12- Table number 1 is not clear. It should be edited.

reviewer 2:
1. The manuscript should be rechecked for language quality.
2. In the Abstract (in the methods section), it is not correct to use the expressions IFN1 and IFN2 to indicate the first and second weeks of using interferon.
3. Throughout the article (abstract and …), instead of using the general term interferon, the type of interferon used should be mentioned.
4. In the Abstract (in the results section, lines 23 and 24), INF1 and INF2 should be corrected (IFN) and revised according to objection number 2.
5. In the introduction, the description of the role of interferon in immune responses as well as defense against COVID-19 is inaccurate, and the sources cited in this article have been poorly reviewed.
6. Line 71 does not specify the location and city of the hospital (although it is mentioned later).
7. Lines 75 and 76: What type of interferon did they receive? IFN type 1 (IFNα or IFNβ)? (Although it is mentioned later, in line 80.) Also, grouping patients into IFN1 and IFN2 is incorrect.
8. Information on the use of interferon is incomplete. The type of interferon injection and the day(s) of its injection are not specified. What type of IFNβ is used?
9. Has interferon use been associated with routine treatment?

10. Line 75: What has been the routine treatment?
11. Line 104: CPR is incorrect (CRP).
12. In the results section, percentages should be reported consistently.
13. In the results section, percentages should be reported consistently (in line 115, 60(60.00%) were male and 40% female).
14. Line 122: Correct the placement of the period: “two groups for age and sex. (P-value was 0.12 and 0.17 respectively)”.
15. Line 129: INF1 should be corrected.
16. Line 131: (p=0.02) should be corrected to (P=0.02).
17. Modify the phrase INF in the table title.
18. Why is CT scan not mentioned in the study of the effects of interferon?
19. Line 156: (IFN1=15+12, IFN2=24+16,) should be corrected.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewers' Comments:

Reviewer 1:
1. The manuscript should be re-checked for literary writing.

It was completely rechecked and corrected.

2. In the Abstract (in method section), it is not correct to use the expressions IFN1 and IFN2 to indicate the first and second weeks of using interferon.
3. In the whole article (abstract and ...), instead of using the general term interferon, the type of interferon used should be mentioned.
4. In the Abstract (in results section, lines 23 and 24), INF1 and INF2 should be correct (IFN) and be corrected according to objection number 2.
5. In introduction, the role of interferon in immune responses as well as defense against COVID-19 is inaccurate and the sources cited in this article have been poorly reviewed.
6. Line 71, does not specify the location and city of the hospital (although it is mentioned later).
7. Line 75 and 76, what type of interferon did they receive? IFN type 1 (IFNα or IFNβ)? (although it is mentioned later, line 80). Also, grouping patients into IFN1 and IFN2 is incorrect.

Comments (2-7) ,were all corrected.

8. Information on the use of interferon is incomplete. The type of interferon injection and the day(s) of its injection are not specified. What type of IFNβ is used?

The medication used for these patients was beta1-a interferon (ReciGen®) administered in 44 µg doses (total 12 million units).
It was administered every other day for 5 days.

9. Has interferon use been associated with routine treatment?

Yes, interferon use been associated with routine treatment?

10. Line 75, What has been the routine treatment?

Routine pharmacotherapy according to the National Committee of COVID-19 treatment protocols included: (i) Hydroxychloroquine/chloroquine phosphate: Hydroxychloroquine sulfate tablets 200 mg or chloroquine phosphate tablets 250 mg (equivalent to 150 mg base amount); 2 tablets every 12 hours on the first day and then 1 tablet tabevery 12 hours for at least 7 days and up to 14 days. (ii) One of the following medications at the discretion of the treating physician: Kaletra tablets (lopinavir/ritonavir) 200/50 mg; 2 tablets every 12 hours after meals for at least 7 days and up to 14 days. (iii) Atazanavir/Ritonavir 300/100 tablet: 1 tablet a day with food; or Atazanavir 400 mg daily for a minimum of 7 days and a maximum of 14 days.

11. Line 104, CPR is incorrect (CRP).
12. In the results section, the percentage report should be the same.
13. In the results section, the result percentage report should be written in the same way (in line115, 60(60.00%) were male and 40% female).
14. Line 122, correct the location of the point. two groups for age and sex. (P-value was 0.12 and 0.17 respectively).
15. Line 129, INF1 should be correct.
16. Line 131, (p=0.02) should be correct (P=0.02).
17. Modify the phrase INF in the table title.

Comments (11- 17), were all corrected.

18. Why is CT scan not mentioned in the study of the effects of interferon?

Because we didn’t have sufficient data for it.

19. Line 156, (IFN1=15+12, IFN2=24+16,) should be reformed.

It was changed.

Reviewer 2:
this review is a good practice and has done well and it can publishe without any chang
Reviewer 3:
Dear author/authors
Due to the scientific and grammatical errors in the manuscript entitled “Effect of Interferon in the first week versus the second week of treatment on recovery in patients with COVID-19: A retrospective study”, it is not recommended for acceptance and publication. Some of these errors are listed below:
1- The manuscript should be edited due to the writing and grammatical errors.

It was completely re-checked and corrected for literary writing and grammatical errors.

2- In the abstract section, the following sentence should be edited: “In severe cases, it affects the surface of immune cells and causes inappropriate responses”.

It was edited.

3- The results part in the abstract section should be edited. It is recommended to delete the following sentence: “The study population included 200 patients who were divided into IFN1 (n=100) and IFN2 (n=100) groups. IFN1 had received beta interferon in the first week and IFN2 in the second week of treatment. The two groups’ baseline demographic data were matched”. This should be mentioned in the materials and methods section.

It was changed.

4- It is suggested that the tests performed in this study be listed in the Methods part of abstract section.

They were listed in the Methods part of abstract section.

5- A suitable running title is recommended.

A better title was chosen.

6- All abbreviations used in the manuscript must be written in full format when they used for the first time.

They were all corrected.

7- In the following sentence: “the body’s natural defense mechanism against this infection is hardly activated”, “hardly activated” is not true. It should be changed.

It was changed.

8- In the following sentence: “Interestingly, although rapid production of interferon at the onset of the disease is 55 an important factor for increasing lymphocyte T cells, increase interferon in later 56 stages inhibit T cells or deplete lymphoid tissues of them”, “increasing lymphocyte T cells” is not in correct format.

It was changed.

9- In the following sentence:” The secondary objective was to investigate the difference between IFN1 and IFN2 groups in terms of WBC (White Blood Cell), Hb (Hemoglobin), Urea, LDH (Lactate dehydrogenase), CPR(C - reactive protein) levels and length of hospitalization”, CPR is not true. it should be changed to CRP.

It was corrected.

10- In the statistical methods section, which test was used to analyze the normal distribution of data?

Chi-square test was used for the qualitative parameters and t-test for quantitative ones.It was added to the text.

11- In the results section, the following sentence should be edited:” In our population 58(58.00%) of patients in 124 the first group and 62(62.00%) of patients in the second group were male”.

It was changed.

12- Table number 1 is not clear. It should be edited.

The tables were divided in to two separate tables for better explanation.

2 Revision 1

1 comment · 15 Jan 2022

Editor-in-Chief

MINOR REVISION 15 Jan 2022

dear author
Reviewer 1:
1- Please modify the phrase interferonβ1-a to interferon β1-a (IFNβ1-a) and, in the rest of the text, use the abbreviated phrase IFNβ1-a.
2- In line 53, please replace this phrase: These receptors are found on most of the body's nucleated cells.
Reviewer 2:
The recent format of the manuscript still has some issues that need to be addressed.
1- A suitable running title has not been added.
2- In the results section, the authors declare that a total of 200 patients were admitted to their study. The following is then mentioned: "Sixty patients (60.00%) were male and 40 (40.00%) were female", which indicates that the total number of participants is one hundred. What is the reason for the difference? Also, the format of the mentioned numbers must be the same. These data should be edited in table no. 1.
3- Regarding the data presented in table 1 and table 2, it is mentioned that a P-value >0.05 was considered significant. Is it true?
4- In the statistical section, the following question has not been answered: Which test was used to analyze the normal distribution of the data?

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor-in-chief

Thank you very much for your email dated regarding the preliminary revision of the manuscript. We have complied with all reviewers' comments and hope that the manuscript is now suitable for publication in your valuable journal.

Looking forward to hearing from you at your earliest convenience.

Sincerely yours,

Mitra KazemiJahromi, MD,

Endcrinology and metablism research center, Hormozgan University of Medical Sciences, Bandarabbas, Iran

Response to Reviewe

Reviewers' Comments:

Dear author
Reviewer 1:
1-Please modify the phrase interferonβ1-a to interferon β1-a (IFNβ1-a) and in the rest of the text, use the abbreviated phrase IFNβ1-a.

A: It was corrected in every part of the manuscript.

2- In line 53, please replace this phrase.: These receptors are found on most of the body's nucleated cells.

A: It was corrected.

Reviewer 2:
The recent format of the manuscript still has some issues that need to be addressed.
1- A suitable running title is not added.

A: It was added.

2- In the results section, the authors declare that a total of 200 patients admitted in their study. At the following it is mentioned that Sixty patients (60.00%) were male and 40

(40.00%) were female Which represents the total number of participants is one hundred. What is the reason for the difference? Also, the format of the mentioned numbers must be the same. These data should be edited in table no.1.

A: Yes, we had 200 participants, (100 in (IFN week1 and 100 in IFN week2 groups). The percentages were corrected.

3- Regarding the data presented in table 1 and table 2, it is mentioned that the P-value >0.05 was considered significant. Is it true?

A: Certainly, it was a mistake in typing and it was corrected.

4- In the statistical section, this question has not been answered that which test was used to analyze the normal distribution of data?

A: We used chi-square test for the qualitative parameters and independent t-test for quantitative ones to analyze the normal distribution of the data.

3 Revision 2

1 comment · 29 Jan 2022

Editor-in-Chief

MINOR REVISION 29 Jan 2022

Dear Author
Reviewer1:
1- Modify the title: Effects of interferon β-1a administration in the first vs. second week of treatment on recovery in patients with COVID-19: A retrospective study
2- In the Abstract, in the method section (in line 12): change (IFNβ1-a) to interferon β1-a (IFNβ1-a)
3- In lines 14, 20, 26 and 28: change (IFNβ1-a) to IFNβ1-a
4- In line 30: change (IFNβ1-a) to interferon β1-a (IFNβ1-a)
5- In line 55: change replication. (7) to replication (7).
6- In lines 79, 81, 114, 155, 160, 165, 168, 170 and 203: change (IFNβ1-a) to IFNβ1-a
7- In the title of Table 2: change (IFNβ1-a) to IFNβ1-a
Reviewer2:
I thank the authors for their answers and corrections. Given that most of the issues raised in the text of the article have been addressed, this article is recommended for acceptance and publication. Only in the statistical analysis section, it should be stated that the Kolmogorov-Smirnov test was used to examine the normal distribution of data.

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewer 1:
Dear authors, please correct the following:
1- Modify the title: Effects of interferon β-1a administration in the first vs. second week of treatment on recovery in patients with COVID-19: A retrospective study
2- In the Abstract, in the method section (in line 12): (IFNβ1-a) modify to interferon β1-a (IFNβ1-a)
3- In lines 14, 20, 26 and 28: (IFNβ1-a) modify to IFNβ1-a
4- In line 30: (IFNβ1-a) modify to interferon β1-a (IFNβ1-a)
5- In line 55: replication. (7) modify to replication (7).
6- In lines 79, 81, 114, 155, 160, 165, 168, 170 and 203: (IFNβ1-a) modify to IFNβ1-a
7- In the title of Table 2: (IFNβ1-a) modify to IFNβ1-a

Answer: All the changes were made.

Reviewer 2:
Thanks the authors for their answers and corrections. Given that most of the issues raised in the text of the article have been modified, this article is recommended for acceptance and publication. Only in the statistical analysis section it should be written that Kolmogorov-Smirnov test was used to examine the normal distribution of data.

Answer: Thank you so much. We substitute this method for the analysis of the normal distribution of data.

4 Revision 3

1 comment · 10 Feb 2022

Editor-in-Chief

MINOR REVISION 10 Feb 2022

Dear author/authors,
Please correct the following:
- Wherever interferon is abbreviated, please use the format IFNβ1-a. In the following instances, this term is written as INFβ1-a:
- On lines: 12- 14- 20- 26- 27- 30- 79- 80- 114- 141- title of table 2- 155- 160- 165- 168- 170 and 203
****

Dear authors, please correct the following:
On lines 12, 14, 20, 26, 27, 30, 79, 80, 114, 141, in the title of table 2, and on lines 155, 160, 165, 168, 170 and 203, change INFβ1-a to IFNβ1-a.

5

Revision 4

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewers' Comments:

Dear authors, please correct the following:
In lines 12,14, 20, 26, 27, 30, 79, 80, 114, 141, in table 2 title, 155, 160, 165, 168, 170 and 203: INFβ1-a modify to IFNβ1-a

Answer: In all the lines 12,14, 20, 26, 27, 30, 79, 80, 114, 141, in table 2 title, 155, 160, 165, 168, 170 and 203, INFβ1-a was changed to IFNβ1-a

EIC comments:

In lines 12,14, 20, 26, 27, 30, 79, 80, 114, 141, in table 2 title, 155, 160, 165, 168, 170 and 203: INFβ1-a modify to IFNβ1-a

Answer: In all the lines 12,14, 20, 26, 27, 30, 79, 80, 114, 141, in table 2 title, 155, 160, 165, 168, 170 and 203, INFβ1-a was changed to IFNβ1-a

5 Revision 4

1 comment · 28 Feb 2022

Editor-in-Chief

ACCEPT 28 Feb 2022

Dear Author
Congratulations!
Hereby we announce that your manuscript entitled "Effect of Interferon in the first week versus the second week of treatment on recovery in patients with COVID-19: A retrospective study" has been accepted for publication in the International Journal of Infection.
The manuscript will be available online in future issues.
Wish you all the best