

# SARS CoV 2 Infection and the possible implication of low dose irradiation: A perspective

Dr. Sara Taleb

Department of Pharmacology and Toxicology, Faculty of Medicine and Pharmacy, University Hassan II, Casablanca, Morocco.

## Abstract:

Severe Acute Respiratory Syndrome due to 2019 novel coronavirus emerged in Wuhan and rapidly spread throughout the world; pandemic state was therefore declared. Although the majority of patients are asymptomatic, severe forms of pneumonia can be observed altering patient's prognosis. Historical studies have attested to efficiency of low dose X rays irradiation in viral pneumonia. This could be explained by the anti-inflammatory effect of low dose irradiation on immune system. Pneumonia due to SARS-Cov2 could be better controlled by low dose irradiation at the onset of respiratory signs. Clinical studies should be conducted to establish the risk-benefit ratio and to determine the optimal irradiation modalities.

**Keywords :** Radiation exposure, Low dose irradiation, Pneumonia, Immune system, SARS-CoV-2, Coronavirus.

## I- Introduction :

Severe Acute Respiratory Syndrome (SARS) is an infectious disease first observed in 2002 in southern China. SARS is caused by a pathogen called SARS-associated to coronavirus (SARS-Cov), a previously unknown virus in the coronavirus family [1].

In December, 2019, series of pneumonia cases of an unknown cause emerged in Wuhan, China, with clinical presentations resembling to a viral pneumonia. Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus, which was named 2019 novel coronavirus (SARS-CoV2) [2].

The World Health Organization has declared on March 2020 that the novel coronavirus is a global pandemic [3]. This pandemic present a challenge to identify effective treatment modalities.

The symptoms presented by the affected subjects range from asymptomatic or mild flu-like symptoms to more critical symptoms including respiratory distress and multivisceral failure that can lead to death [2].

Given the increasing number of cases escaping control under current guideline recommended treatments, other therapies must be explored to improve the response of critical patients.

Kirkby and Mackenzie was the first author to discuss the possible therapeutic effect of low dose radiation (LDR) in SARS-CoV2 pneumonia patients and suggested this forgotten therapeutic approach [4].



The aim of this study was to review the beneficial effect of LDR as a potential treatment in the context of SARS-CoV2 pneumonia and to explain the potential mechanisms involved.

## **II- Methods :**

A bibliographic screening was conducted using different databases: Science direct, PubMed, to identify English articles published up to July 25, 2020, using search words: Irradiation ; Radiation exposure ; Pneumonia ; Immune system ; SARS-CoV-2 ; COVID-19 ; Coronavirus.. Other articles cited in the bibliographic articles were used in the development of this review.

## **III- Results and Discussion :**

Pneumonia occurs as an inflammatory immune response to an infection where the alveoli ignite and secrete fluid compromising their gas exchange function. In a viral infection, viruses trigger immune cells to synthesize pro-inflammatory cytokines and chemokines [5], prompting the immune response.

Historical studies evaluated the impact of LDR in pneumonia. Several studies were conducted to assess ionizing radiation as a potential therapeutic modality for bacterial and viral pneumonia during the first half of the 20th century [6], including the ones published by Rousseau [7] and Oppenheimer and their colleagues [8] who established that low-dose irradiation improved the symptomatology of patients with severe viral pneumonia. Although the low number of patients, (29 and 56 patients) the rate of positive responses was high (22 and 45 remission patients respectively).

Other authors reported a lower risk of mortality from severe viral pneumonia in mice receiving low dose radiation. Indeed, a dose of 0.04 Gy administered 24 hours after the onset of symptoms may have shortened the acute phase with reduced mortality by half[9]. Similar results were observed at a dose of 0.9 Gy 48 hours after inoculation [10]. However, these studies were too old and were not conducted with sufficient scientific reliability [11].

Two recent clinical trials have attempted to evaluate low-dose irradiation in patients with SARS-CoV2 pneumonia. The first pilot trial named RESCUE 1-19 was published in a nonepeer-reviewed journal [12]. Five patients with SARS-CoV2 pneumonia received whole-lung irradiation with a single-fraction of 1.5 Gy. Eighty percent of them recovered rapidly and were weaned from supplemental oxygen at a mean time of 1.5 days. In all patients, no acute toxicity regarding LDR was reported.

The second clinical trial was conducted in Iran, five patients were treated with whole-lung irradiation in a single fraction of 0.5 Gy. They were followed for 5 to 7 days to evaluate the response to treatment and toxicities.



They also achieved a treatment response rate of 80%. Thereby, whole-lung irradiation in a single fraction of 0.5 Gy had encouraging results in oxygen-dependent patients with SARS-CoV2 pneumonia [13].

While there are consistent findings supporting therapeutic role of LDR in the treatment of SARS-Cov2 pneumonia, the question remains how to reactivate an established but old hypothesis in the context of the current pandemic, and try to explain the mechanisms of action.

SARS-Cov2 induces immune responses that vary from a patient to another. In healthy carriers the inflammatory response appears weaker. On the opposite, in patients with more serious symptoms, inflammatory phenomena are increased. A study of 41 patients with severe forms of infection found high levels of pro-inflammatory cytokines, including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF  $\alpha$  [13]. This “cytokine storm” is thought to be the inducer of viral sepsis and lung damage that can be complicated by acute respiratory distress syndrome, multivisceral failure and death.

The repercussions of ionizing radiation on the immune system are multifactorial and highly dependent on radiation doses and modalities; whereas high dose radiation ( $> 2\text{Gy}$  per fraction) causes an increased inflammatory response [14]; lower dose (1Gy) are associated with an anti-inflammatory effect [15].

Anti-inflammatory action of LDR is a new concept with increasingly widespread therapeutic applications. Indeed, low-dose radiation therapy is often used effectively in the treatment of benign inflammatory diseases, especially in the acute phase. However, the underlying mechanisms are not fully explored [16]. Several in vivo and in vitro studies have reported, the efficiency of LDR in immune response regulation : leukocyte apoptosis induction [17]; reduction in reactive oxygen species [18], iNOS pathway limitation [19]; decreased secretion of chemokine (CCL20) [20] and pro-inflammatory cytokines (including IL-1 $\beta$  and Tnf $\alpha$ ) [21] and reduced expression of MAPK (p38, Akt) were reported. These data could help explain the anti-inflammatory phenomena of LDR (Figure 1).

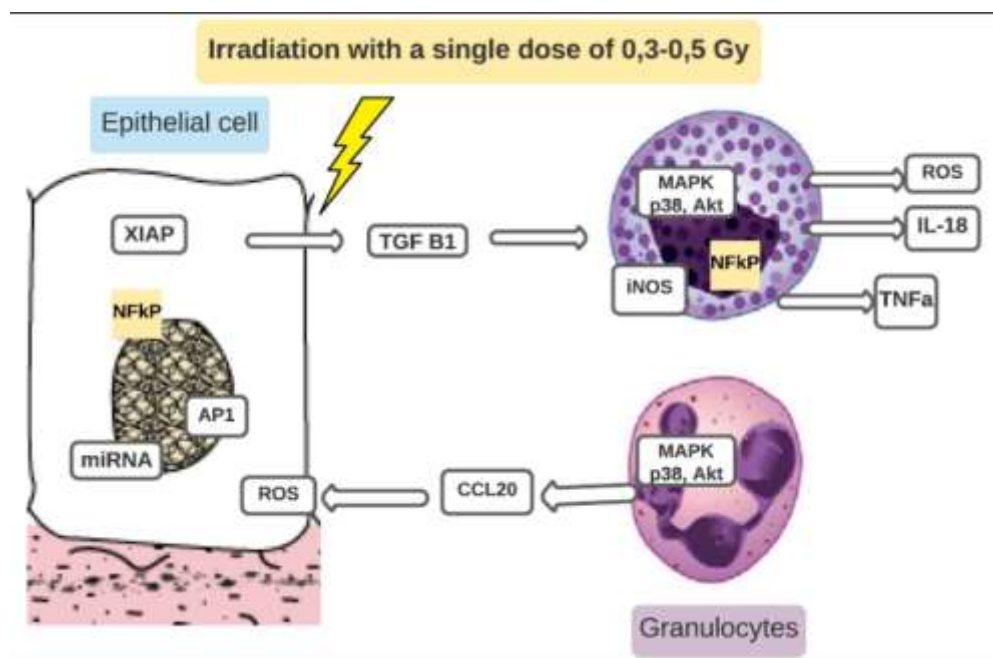
Although low-dose irradiation cannot act by killing the causative agent as an antiviral, its anti-inflammatory function could improve patient tolerance and promote the effectiveness of other therapeutics [22].

Pneumonia due to SARS-Cov2 could be better controlled by low-dose radiation at the onset of respiratory signs. Severe forms may also be less frequent. In the other hand, too early irradiation (in asymptomatic subjects or with flu-like symptoms) could disrupt the immune system fighting against the virus and delay its elimination.

It is also necessary to clarify that anti-inflammatory effects of LDR are not limited to the irradiation site and may cause systemic effects [6]. Therefore, it would not be necessary to irradiate the lungs in order to obtain anti-inflammatory effect, but to perform a whole body low dose irradiation. The common toxicities of radiation therapy would be avoided.



In conclusion, it would be necessary to evaluate the effects of LDR on SARS-Cov2 carriers largest clinical studies; in order to establish the risk-benefit ratio and to determine the optimal irradiation modalities.



**Figure 1: Factors involved in local anti-inflammatory activity of LDR after exposure of activated epithelial cells at a dose of 0.3–0.5 Gy.**

## REFERENCES

- [1] D. Benvenuto, M. Giovanetti, A. Ciccozzi, S. Spoto, S. Angeletti, et M. Ciccozzi, « The 2019-new coronavirus epidemic: Evidence for virus evolution », *J. Med. Virol.*, vol. 92, n° 4, p. 455-459, 2020, doi: 10.1002/jmv.25688.
- [2] C. Huang *et al.*, « Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China », *The Lancet*, vol. 395, n° 10223, p. 497-506, févr. 2020, doi: 10.1016/S0140-6736(20)30183-5.
- [3] D. Cucinotta et M. Vanelli, « WHO Declares COVID-19 a Pandemic », *Acta Bio-Medica Atenei Parm.*, vol. 91, n° 1, p. 157-160, 19 2020, doi: 10.23750/abm.v91i1.9397.
- [4] C. Kirkby et M. Mackenzie, « Is low dose radiation therapy a potential treatment for COVID-19 pneumonia? », *Radiother. Oncol.*, vol. 0, n° 0, avr. 2020, doi: 10.1016/j.radonc.2020.04.004.
- [5] B. Moldoveanu *et al.*, « Inflammatory mechanisms in the lung », *J. Inflamm. Res.*, vol. 2, p. 1-11, déc. 2008.
- [6] E. J. Calabrese et G. Dhawan, « How Radiotherapy Was Historically Used To Treat Pneumonia: Could It Be Useful Today? », *Yale J. Biol. Med.*, vol. 86, n° 4, p. 555-570, déc. 2013.
- [7] J. P. Rousseau, W. M. Johnson, et G. T. Harrell, « The Value of Roentgen Therapy in Pneumonia Which Fails to Respond to the Sulfonamides », *Radiology*, vol. 38, n° 3, p. 281-289, mars 1942, doi: 10.1148/38.3.281.
- [8] « Oppenheimer: Roentgen Therapy of Virus Pneumonia - Google Scholar ». [https://scholar.google.com/scholar\\_lookup?journal=Am+J+Roentgenol+&+Rad+Therapy&title=Roentgen+therapy+of+%E2%80%9Cvirus%E2%80%9D+pneumonia&author=A+Oppenheimer&volume=49&publication\\_year=1943&pages=635-638&](https://scholar.google.com/scholar_lookup?journal=Am+J+Roentgenol+&+Rad+Therapy&title=Roentgen+therapy+of+%E2%80%9Cvirus%E2%80%9D+pneumonia&author=A+Oppenheimer&volume=49&publication_year=1943&pages=635-638&) (consulté le avr. 27, 2020).
- [9] G. J. Baylin, I. N. Dubin, et W. G. Gobel, « The effect of roentgen therapy on experimental virus pneumonia; on feline virus pneumonia », *Am. J. Roentgenol. Radium Ther.*, vol. 55, p. 473-477, avr. 1946.



- [10] I. N. Dubin, G. J. Baylin, et W. G. Gobble, « The effect of roentgen therapy on experimental virus pneumonia; on pneumonia produced in white mice by swine influenza virus », *Am. J. Roentgenol. Radium Ther.*, vol. 55, p. 478-481, avr. 1946.
- [11] A. Kefayat et F. Ghahremani, « Low dose radiation therapy for COVID-19 pneumonia: A double-edged sword », *Radiother. Oncol.*, vol. 147, p. 224-225, juin 2020, doi: 10.1016/j.radonc.2020.04.026.
- [12] C. B. Hess *et al.*, « Low-Dose Whole-Lung Radiation for COVID-19 Pneumonia: Planned Day-7 Interim Analysis of a Registered Clinical Trial », *medRxiv*, p. 2020.06.03.20116988, juin 2020, doi: 10.1101/2020.06.03.20116988.
- [13] A. Ameri *et al.*, « Low-Dose Whole-Lung Irradiation for COVID-19 Pneumonia: Short Course Results », *Int. J. Radiat. Oncol.*, p. S0360301620314450, juill. 2020, doi: 10.1016/j.ijrobp.2020.07.026.
- [14] « Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic », *Asian Pac. J. Allergy Immunol.*, 2020, doi: 10.12932/AP-200220-0772.
- [15] J. Williams, Y. Chen, P. Rubin, J. Finkelstein, et P. Okunieff, « The biological basis of a comprehensive grading system for the adverse effects of cancer treatment », *Semin. Radiat. Oncol.*, vol. 13, n° 3, p. 182-188, juill. 2003, doi: 10.1016/S1053-4296(03)00045-6.
- [16] F. Rödel *et al.*, « Modulation of inflammatory immune reactions by low-dose ionizing radiation: molecular mechanisms and clinical application », *Curr. Med. Chem.*, vol. 19, n° 12, p. 1741-1750, 2012, doi: 10.2174/092986712800099866.
- [17] F. Rödel, B. Frey, G. Multhoff, et U. Gaipl, « Contribution of the immune system to bystander and non-targeted effects of ionizing radiation », *Cancer Lett.*, vol. 356, n° 1, p. 105-113, janv. 2015, doi: 10.1016/j.canlet.2013.09.015.
- [18] P. Belloni, P. Latini, et F. Palitti, « Radiation-induced bystander effect in healthy G0 human lymphocytes: Biological and clinical significance », *Mutat. Res. Mol. Mech. Mutagen.*, vol. 713, n° 1, p. 32-38, août 2011, doi: 10.1016/j.mrfmmm.2011.05.010.
- [19] T. Criswell, K. Leskov, S. Miyamoto, G. Luo, et D. A. Boothman, « Transcription factors activated in mammalian cells after clinically relevant doses of ionizing radiation », *Oncogene*, vol. 22, n° 37, Art. n° 37, sept. 2003, doi: 10.1038/sj.onc.1206680.
- [20] G. Hildebrandt, M. P. Seed, C. N. Freemantle, C. A. Alam, P. R. Colville-Nash, et K. R. Trott, « Mechanisms of the anti-inflammatory activity of low-dose radiation therapy », *Int. J. Radiat. Biol.*, vol. 74, n° 3, p. 367-378, sept. 1998, doi: 10.1080/095530098141500.
- [21] F. Rödel *et al.*, « The anti-inflammatory effect of low-dose radiation therapy involves a diminished CCL20 chemokine expression and granulocyte/endothelial cell adhesion », *Strahlenther. Onkol. Organ Dtsch. Rontgengesellschaft Al*, vol. 184, n° 1, p. 41-47, janv. 2008, doi: 10.1007/s00066-008-1776-8.
- [22] B. Frischholz *et al.*, « Reduced secretion of the inflammatory cytokine IL-1 $\beta$  by stimulated peritoneal macrophages of radiosensitive Balb/c mice after exposure to 0.5 or 0.7 Gy of ionizing radiation », *Autoimmunity*, vol. 46, n° 5, p. 323-328, août 2013, doi: 10.3109/08916934.2012.747522.
- [23] S. Iordanskiy *et al.*, « Therapeutic doses of irradiation activate viral transcription and induce apoptosis in HIV-1 infected cells », *Virology*, vol. 485, p. 1-15, nov. 2015, doi: 10.1016/j.virol.2015.06.021.