

**LETTER TO THE EDITOR**

# Interferon: The invisible link in the physiopathology of COVID-19 and BCGitis?

Dear editor,

Facing the COVID-19 pandemic, we were intrigued by the difference of incidence and disease severity between men and women (60%-70% of deaths occurring in men). This disparity remains significant even after age stratification in all age groups (postmenopausal women vs age-matched men), suggesting a partially hormone-independent mechanism.

Coincidentally, during the last month we were reviewing the infectious complications of Bacillus Calmette-Guerin (BCG) bladder instillation. BCG is used for non-muscle-invasive bladder cancer (NMIBC) after standard surgical treatment: surprisingly, among 243 BCGitis cases reported in the literature, only three were female.

The higher number of BCGitis in men has been justified so far considering the worldwide M/F ratio for bladder cancer (3.5:1).<sup>1</sup> In addition, for anatomical reasons, traumatic catheterization is more common in men, potentially providing a wider port of entry for systemic BCG dissemination.<sup>2</sup> However, these two issues are not strong enough to justify the overwhelming unbalanced gender ratio found in BCGitis (M/F 49:1).

Bacillus Calmette-Guerin acts against NMIBC mainly by stimulating non-specific immune response and a torrent of Th-1 cytokines, including IFN- $\gamma$ .<sup>3</sup> IFN- $\gamma$  plays a role against intracellular infection by pathogens such as *Mycobacterium tuberculosis* and *Mycobacterium bovis*.<sup>4</sup> A reduced level of IFN- $\gamma$  has been observed in men, both prior than after surgery.<sup>5</sup>

Bacillus Calmette-Guerin used as a tubercular vaccine is generally administered to young patients and induced IgG

and IFN $\gamma$  generally diminish with age if a booster dose is not given.<sup>4</sup> On the contrary, BCG used as immune therapy for non-muscle-invasive bladder cancer is administered to adult elderly patients, and according to the schedule of the treatment, the instillations are repeated periodically resulting in a more sustained immune response.

Constitutional differences in male and female immune systems have long been described. The underlying biological mechanisms are not fully understood. They are supposed to result from steroid hormones secreted by gonads and/or different cytokines response.

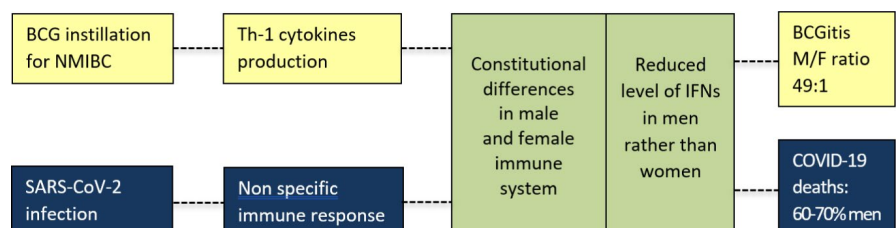
With regard to steroid hormones, *in vivo* studies<sup>6-8</sup> reported a protective role of oestrogens against respiratory infections. For instance, high levels of 17 $\beta$ -estradiol are related to better clinical outcomes in mice infected with influenza A.<sup>6</sup>


Inflammatory immune responses, as well as the number and activity of innate immune cells, are higher in women. Human studies demonstrated that plasmacytoid dendritic cells of woman exhibit increased expression of interferon (IFN)- $\alpha$ , following toll-like receptor (TLR)-7 stimulation.<sup>9</sup> Furthermore, TLR-associated genes that activate IFN pathway are significantly upregulated in woman after vaccinations.<sup>10</sup>

To be kept in mind, both *in vitro* and *in vivo* studies demonstrated the efficient role of IFNs against SARS-CoV.<sup>11,12</sup>

In light of the above, we hypothesize that major susceptibility of male gender to COVID-19 and to BCG infection might share a common interferon-centred physiopathological basis that needs to be deeply investigated (Figure 1).

**FIGURE 1** Schematic diagram of the hypothesized common mechanism for gender disparity in BCGitis and COVID-19



Stefano Di Bella<sup>1</sup>  
Paolo Cabas<sup>2</sup>   
Roberta Maria Antonello<sup>3</sup>  
Michele Rizzo<sup>2</sup>

<sup>1</sup>Department of Infectious Disease, Maggiore Hospital, University of Trieste, Trieste, Italy

<sup>2</sup>Department of Urology, Cattinara Hospital, University of Trieste, Trieste, Italy

<sup>3</sup>University of Trieste, Trieste, Italy

### Correspondence

Paolo Cabas, Department of Urology, Cattinara Hospital, University of Trieste, Strada di Fiume 447, Trieste, 34149, Italy.

Email: paolo.cabas@asuits.sanita.fvg.it

### ORCID

Paolo Cabas  <https://orcid.org/0000-0001-5978-0388>

### REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. Wiley-Liss Inc. 2015;136:E359-E386.
2. Decaestecker K, Oosterlinck W. Managing the adverse events of intravesical bacillus Calmette-Guèrin therapy. *Res. Reports Urol*. Dove Medical Press Ltd. 2015;157-163.
3. Alhunaidi O, Zlotta AR. The use of intravesical BCG in urothelial carcinoma of the bladder. *Ecancermedicalscience*. 2019;13:905. <https://doi.org/10.3332/ecancer.2019.905>
4. Husain AA, Dagainawla HF, Singh L, Kashyap RS. Assessment of immunological markers and booster effects of Ag85B peptides, Ag85B, and BCG in blood of BCG vaccinated children: a preliminary report. *Clin Exp Vaccine Res*. Korean Vaccine Society (KAMJE). 2016;5:31.
5. Ono S, Tsujimoto H, Hiraki SI, Takahata R, Kinoshita M, Mochizuki H. Sex differences in cytokine production and surface antigen expression of peripheral blood mononuclear cells after surgery. *Am J Surg*. 2005;190:439-444.
6. Robinson DP, Lorenzo ME, Jian W, Klein SL. Elevated 17 $\beta$ -estradiol protects females from influenza a virus pathogenesis by suppressing inflammatory responses. *PLoS Pathogens*. 2011;7(7):e1002149. Public Library of Science.
7. Hao S, Zhao J, Zhou J, Zhao S, Hu Y, Hou Y. Modulation of 17 $\beta$ -estradiol on the number and cytotoxicity of NK cells in vivo related to MCM and activating receptors. *Int Immunopharmacol* [Internet]. 2007;7:1765-1775.
8. Bengtsson ÅK, Ryan EJ, Giordano D, Magaletti DM, Clark EA. 17 $\beta$ -estradiol (E2) modulates cytokine and chemokine expression in human monocyte-derived dendritic cells. *Blood* [Internet]. 2004;104:1404-1410.
9. Ziegler SM, Altfeld M. Human immunodeficiency virus 1 and type I interferons-where sex makes a difference. *Front Immunol*. Frontiers Media S.A. 2017;8:1224.
10. Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. *Lancet Infect Dis*. 2010;10(5):338-349.
11. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human interferons. *Lancet*. Elsevier Limited. 2003;362:293-294.
12. Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. *J Am Med Assoc* [Internet]. 2003;290(24):3222.