

## Interleukin-2 Induced Atrioventricular Dissociation

Shridhar P<sup>1\*</sup>, Lasorda D<sup>2</sup>, Chun YJ<sup>1,3,4</sup>

<sup>1</sup>Department of Bioengineering, University of Pittsburgh, Pittsburgh, USA

<sup>2</sup>Department of Cardiology, Allegheny General Hospital, Pittsburgh, USA

<sup>3</sup>Department of Industrial Engineering, University of Pittsburgh, Pittsburgh, USA

<sup>4</sup>McGowan Institute for Regenerative Medicine, Pittsburgh, USA

\* **Corresponding author:** Shridhar P, Department of Bioengineering, University of Pittsburgh, Pittsburgh, USA, E-mail: pus8@pitt.edu

---

### Editorial

Interleukin-2 (IL2) is a cytokine with immunogenic and anti-antigenic properties.<sup>1</sup> Recombinant Interleukin-2 is approved by FDA for the treatment of metastatic renal cell carcinoma and metastatic melanoma.<sup>2</sup> IL-2 is also believed to be useful in managing psoriasis and inflammatory bowel disease. IL2 is commonly associated with cardiac toxicity including arrhythmias (classically tachyarrhythmia), hypotension and myocarditis.<sup>3</sup>

The exact mechanism of IL-2 causing heart block is unknown. It has been likened to a class I antiarrhythmic agent due to its action on sodium ion channels in cardiac myocytes. Some authors have postulated that capillary leak syndrome could possibly explain arrhythmogenic properties of IL-2. Transient dose-dependent lymphoid infiltration of the atrioventricular node or the conduction system of the heart might lead to this IL-2 toxicity. There is recent evidence of increased IL-2 in patients with Sjogren's syndrome who have higher rate of congenital heart blocks.<sup>4</sup>

Although there is higher incidence of tachyarrhythmia, there is relatively low incidence of heart blocks with IL-2. Isolated cases linking IL-2 to I-II degree block and III degree block have been reported in the last 25 years.<sup>5,6</sup> At least one case of left posterior fascicular due to high dose IL-2 was found in the literature.<sup>7</sup> All these reports observed that atrioventricular conduction defects caused by IL-2 were transient, benign and reversible in previously normal patients. We suggest cautious use of IL-2 in patients with predisposing factors who are at risk for heart block. It should be contraindicated in patients already diagnosed with heart block. Discontinuation of the treatment, along with possible need for dopamine infusion, remains the mainstay for the therapy.<sup>6</sup> Close telemetric monitoring is highly recommended.

On the basis of previous reports, we propose that the contraindication guidelines for IL-2 therapy be revisited based on further evolution of research and clinical experience. Regardless, medical professionals should remain informed of this adverse event. In addition, experimental studies should be designed if we are to understand the exact role of interleukins in conduction heart blocks.

### References

1. White RL., Schwartzentruber DJ., Guleria A., MacFarlane MP., White DE., et al. Cardiopulmonary toxicity of treatment with high dose interleukin-2 in 199 consecutive patients with metastatic melanoma or renal cell carcinoma. *Cancer* 1994; 74: 3212-3222.

2. Gill D., Hahn AW., Sonpavde G., Agarwal N. Immunotherapy of advanced renal cell carcinoma: Current and future therapies. *Hum Vaccin Immunother* 2016; 5: 0.
3. Hannan R., Ishihara D., Louder K., Ahn C., Margulis V., et al. Phase II trial of high-dose interleukin-2 (IL-2) and stereotactic radiation therapy (SABR) for metastatic clear cell renal cell carcinoma (ccRCC): Interim analysis. In ASCO Annual Meeting Proceedings 2016.
4. Ishii T., Ohnuma K., Murakami A., Takasawa N., Yamochi T., et al. SS-A/Ro52, an autoantigen involved in CD28-mediated IL-2 production. *J Immunol* 2003; 170: 3653-3661.
5. Vaitkus PT., Grossman D., Fox KR., McEvoy MD., Doherty JU. Complete heart block due to interleukin-2 therapy. *Am Heart J* 1990; 119: 978-980.
6. Landonio G., Granata D., Baiocchi C. Atrioventricular block following therapy with recombinant interleukin 2. *J Ital Cardiol* 1991; 21: 691.
7. Singla A., Denmeade SR. Left posterior fascicular block due to high-dose interleukin-2. *Ann Pharmacother* 2008; 42: 1340-1343.