

# Role of bevacizumab in juvenile onset recurrent respiratory papillomatosis

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## Abstract

Juvenile-onset recurrent respiratory papillomatosis is a childhood disease notorious for its propensity for recurrence. The children are put through the trauma of repeated surgical procedures affecting the physical and emotional quality of life. Many adjuvant therapies are tried to prevent recurrence of the disease after surgical treatment. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor, which has been recently added to the armamentarium of adjuvant therapy. The present study tries to review the various studies in English literature evaluating the role of bevacizumab in Juvenile-onset recurrent respiratory papillomatosis.

## Introduction

Juvenile-onset recurrent respiratory papillomatosis (JORRP) is a chronic infection of viral etiology affecting the upper aerodigestive tract characterized by proliferative lesions over the mucosa. It is due to human papilloma infections acquired from the birth canal of the mother. Even though it has more predilections for the larynx, it can present at any site in the respiratory tract [1,2]. The disease is usually benign, but often has a high chance of recurrence, which is usually attributed to incomplete surgical removal of the causative virus. Malignant transformation has been reported to occur in long-standing cases [3].

To prevent recurrence adjuvant therapy is advised after definitive surgical treatment. Many agents are suggested for as adjuvant therapy including cidofovir, SGN-00101, interferon, indole-3-carbinole, cis-retinoic acid, mumps vaccine, HspE7, photodynamic therapy etc. There has been evidence that vascular endothelial growth factor receptor plays an important role in the development of recurrent respiratory papillomatosis. Bevacizumab is a recombinant monoclonal immunoglobulin antibody, which inhibits the biologic activity of human vascular endothelial growth factor there by preventing receptor activation. The present study tries to review the English literature regarding the role of bevacizumab in JORRP.

## Methodology

A comprehensive literature review was done in PubMed using the medical terms juvenile onset recurrent respiratory papillomatosis AND Bevacizumab. That article which was general discussion, non-English language and off-topic were removed. The articles, which dealt with the same topic in the references of these articles, were included in the study (Figure 1).

## Results

The initial search in PubMed using medical terms juvenile onset recurrent respiratory papillomatosis and Bevacizumab revealed 10 articles. After initial scrutiny, 4 articles were included in the study after excluding one German article, 3 off topic articles, and 2 general

discussions. One article of the similar topic was included in the study for the references. In the end, there were 5 articles for study (Table 1).

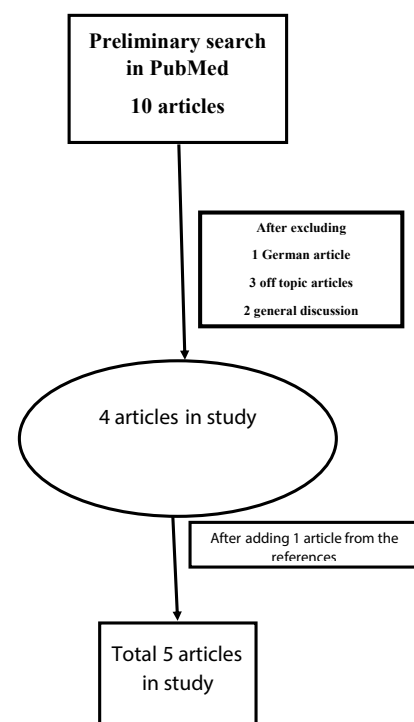


Figure 1:

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**Table 1.** Studies included in the review. KTP- potassium titanyl phosphate PR- Partial response, VGPR- very good partial response, PVQOL -Pediatric Voice Quality of Life.

S. No	Author	Study	Mode of delivery	Outcome measures
1	Mohr <i>et al.</i> [5]	Prospective observational	systemic	PR/VGPF in 5/5 patient Reduction of number of intervention from 18 to 1
2	Sidell <i>et al.</i> [6]	Prospective observational	Sublesional + KTP Laser	Increased time period between interventions 58% improvement in Derkey score
3	Roger <i>et al.</i> [8]	Prospective observational	Intralesional + KTP Laser	Median duration of time between surgical procedures increased by 5.9 weeks (P = .002). Median number of procedures/year decreased by 4 (P = .002). Derkey staging decreased by 6 (P = .03) Median total PVRQOL score increased by 25.5 (P = .02) Median Emotional PVRQOL score increased by 11.3 (P = .047) Median Physical PVRQOL score increased by 14.3 (P = .047).
4	Zeitel <i>et al.</i> [7]	Prospective observational	Sublesional + KTP Laser	3/20 no disease 16/20 reduced disease 1/20 increased disease 35% did not require further Laser procedure compared to 15% in laser only group
5	Maturo <i>et al.</i> [9]	Prospective observational	Microdebrider+KTP Laser + Intralesional	Mean surgical procedure per month was reduced in all 3 patient. Derkey score reduced in 1 patient. PVRQOL increased in 2 patient.

## Discussion

Juvenile-onset recurrent respiratory papillomatosis is benign, but troublesome disease due to its propensity for recurrence and need for multiple surgical procedures. To reduce recurrences the patient is started on adjuvant therapy. Many agents have been tried for adjuvant therapy. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF). Studies have shown strong expression of VEGF-A mRNA was noted in the squamous epithelium of papillomas and VEGFR-1 and VEGFR-2 were noted in the endothelial cells of the underlying vessels [4].

In a Prospective observational study by Mohr *et al.* [5], immediate and sustained response was seen after systemically administering bevacizumab was observed in five patients with progressive JORRP who underwent multiple local procedures. Another significant observation was that 4 out of 5 patients did not require any further surgical intervention. One patient underwent laryngectomy due to malignant transformation. They recorded the response of the lesion to treatment during the administration of the drug and those patients who showed relapse on discontinuation of the drug showed a response on retreatment. Sidell *et al.* [6] demonstrated a median 58% improvement in 5 patients who underwent sub epithelial injections of bevacizumab along with KTP LASER ablation. Another study by Zeitel *et al.* [7] combining sub lesional bevacizumab with KTP laser found that there was a significant response to the disease. Out of 20 patients who received 4 injections, 3 had no discernible disease, 16 patients had a partial response and 1 patient had increased disease. 7 of the patients did not require any further laser coagulation. In a prospective case series by Roger *et al.* [8], intra lesional injection of bevacizumab alone produced an average increase of 5.9 weeks in the time interval between the injections, the median number of surgical interventions were decreased by 4, physical pediatric voice-related quality of life was increased by 14.3 and median emotional pediatric voice-related quality of life was increased by 11.3. In another study by Maturo *et al.* [9], after treating the patient with microdebrider pulsed KTP laser and intralesional bevacizumab, all children showed increased time interval between prodecures.

A prospective study by Best *et al.* [10] in 43 patients to assess the possible complications of intralesional bevacizumab found that there were no complications associated with laryngeal injection of the drug.

## Conclusion

The review concludes that there is ample evidence to suggest that

bevacizumab is a good agent for adjuvant therapy of JORRP. It is either effective when used systemically or intralesionally alone or along with microdebrider or KTP Laser. However, the adequate duration of treatment has to be evaluated as the disease relapsed when the drug was stopped in some studies. More studies are needed comparing the efficacy of different agents used in adjuvant therapy.

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