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ORIGINAL ARTICLE

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Aggressive recurrent respiratory papillomatosis: A series of five consecutive patients successfully treated with adjuvant intravenous bevacizumab. A single Belgian academic center experience

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Abstract

Background: Recurrent respiratory papillomatosis (RRP) is a currently incurable benign neoplasm caused by human papilloma virus (HPV) infection. It usually reduces voice, respiratory, and general quality of life, and is sometimes life-threatening. Patients usually need repeated operations. The use of adjuvant bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor A, has been described in several case reports, with a good efficacy and safety profile.

Methods: We report the cases of five patients with aggressive RRP who were treated with adjuvant systemic bevacizumab in a single Belgian tertiary center.

Results: A complete response was achieved in four patients after a median of 4.5 months, and a partial response in one. In all cases, the number of surgeries was drastically reduced, and quality of life improved. Toxicity was easily managed.

Conclusions: Systemic bevacizumab seems to be an effective and safe adjuvant treatment for aggressive RRP.

KEYWORDS

benign neoplasm, bevacizumab, human papilloma virus, laryngeal tumor, recurrent respiratory papillomatosis

1 | INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a benign disease characterized by the development of papillomatous lesions throughout the upper aero-digestive tract. Although the larynx is the most common site involved, RRP can also affect the naso- and oropharynx, tracheobronchial tree, and even lung parenchyma, causing cough, hoarseness,

dyspnea, lower quality of life, and a high rate of depression. The natural history is usually unpredictable, ranging from spontaneous remission in a minority of cases to recurrent and aggressive disease requiring multiple surgical procedures. Rarely, RRP can be lethal in case of airway obstruction or malignant transformation, which occurs in 3%–7% of adult cases. In addition to its human cost, RRP is also the costliest benign airway neoplasm in the United States, where its annual cost is estimated to be $120 million (approximately $60 000 per patient annually).[1–3]

RRP is caused by human papilloma virus (HPV) infection. Although more than 180 HPV genotypes are known, 90% of RRP cases are related to subtypes 6 and 11. These subtypes are considered low risk because of their weak potential to induce malignant transformation, even though subtype 11 usually induces a more aggressive presentation. The remaining 10% are related to subtypes 16, 18, 31, 33, and other rarer subtypes. Subtypes 16 and 18 are associated with a higher risk of induced malignancy and the development of squamous cell carcinomas of the cervix, vagina, vulva, anus, penis, and oropharynx.[1,3]

Although RRP is usually considered to affect two age groups—children and young adults (in the third and fourth decades of life)—a study conducted on 639 patients treated between 1998 and 2012 in 12 European centers showed an additional peak around the age of 64.[4]

RRP is the most frequent benign laryngeal neoplasm in children, occurring in 4–4.3 per 100 000 per year, although the incidence has decreased thanks to HPV vaccination. The incidence is a bit lower in adults, at 1.8–2 per 100 000 per year.[1,2,5] In the juvenile form, the virus is probably transmitted through contact with infected secretions during delivery or, more rarely, through the placenta before delivery. This form is usually more aggressive, with higher rates of recurrence. In adults, HPV can be transmitted by oral sex, and preferentially affects men. Some suggest that laryngopharyngeal reflux and coinfection with herpes simplex virus type 2 (HSV-2) could also play a role.[6] The adult form is generally less extensive and has a lower rate of recurrence.[1,3,5]

Currently, the only known preventive strategy is vaccination against HPV. After the implementation of a systemic HPV vaccination program for young women in Australia in 2007 (in order to prevent cervical cancer), the incidence of juvenile RRP has significantly declined form 0.16 per 100 000 in 2012 to 0.02 per 100 000 in 2016 ($p = 0.034$). Currently, the nonavalent vaccine against HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Gardasil®; Merck) is recommended widely in developed countries for boys and girls before they become sexually active. This will probably lead to a decrease in RRP cases, as reported in Australia.[3,5,7]

Unfortunately, there is no curative treatment for RRP. The standard treatment is surgical debulking of the papillomatous lesions—especially by laser surgery—but recurrences are common, and surgery often needs to be repeated to preserve good respiratory and phonation quality. Multiple surgeries can lead to local damage and complications such as laryngeal stenosis, burning of the airways, or tracheo-esophageal fistulae. Tracheostomy is sometimes necessary if there is a great risk of laryngeal obstruction.[1,8,9]

In approximately one patient out of five, the disease cannot be controlled by surgery alone, and adjuvant treatments are required. It is usually admitted that an adjuvant treatment may be considered if surgery is necessary more than 4 times per year, in case of rapid recurrence of papillomatous lesions with risk of airway obstruction, and if the disease has spread to the distal respiratory tree.[1,10]

The majority of adjuvant treatments work by immunomodulation or by inhibition of HPV replication. Interferon is one of the first adjuvant treatments shown to be effective in reducing the growth of papillomatous lesions, but at the cost of significant toxicity (i.e., myelosuppression). The antiviral cidofovir is currently the most used adjuvant treatment for RRP, supported by small prospective and retrospective studies showing good response and excellent tolerance.[11–14] It can be administered intravenously, but intralesional injection is more common.[8] In addition to its preventive role, HPV vaccination can also be used as an adjuvant treatment, although the results are less clear.[5,15]

Agents blocking angiogenesis have already been approved, either alone or in association with chemotherapy, for locally advanced or metastatic cancers such as renal, digestive, and gynecological cancers. Bevacizumab is a recombinant humanized monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A) and preventing it from binding to its receptor, leading to a decrease in the growth of new blood vessels and regression of newly formed vasculature within the tumor. This compromises the tumor's blood supply, preventing tumor growth and even leading to tumor shrinkage.[16,17] A few case reports and series have been published, showing good results with bevacizumab as a local and/or systemic adjuvant treatment for RRP. Here, we report the cases of five consecutive RRP patients treated with adjuvant intravenous bevacizumab at CHU UCL Namur.

2 | CASE REPORTS

The patients were recruited at our center between September 2017 and June 2020. Of these five patients, three had juvenile and two had adult onset RRP. The patients' characteristics are presented in Table 1, and the medical histories before bevacizumab are detailed below.

TABLE 1 Patients' characteristics.

Patients	Year of diagnosis	Age at diagnosis	Sex	Extent of disease	Derkay score before bevacizumab	Number of interventions before bevacizumab	Previous adjuvant treatments	HPV type	HPV vaccination
1	1994	3	F	Larynx Trachea Lung	C: 10 A: 15 T: 25	163 for papillomas Three for complications	Interferon Local + IV cidofovir Mitomycin C Photodynamic therapy	Undetermined	Yes 2012–2017
2	1986	4	M	Larynx	C: 4 A: 9 T: 13	>30 in Africa (from 1986 to 2014) 31 in our center (since 2014)	Local cidofovir	Undetermined	Yes
3	2007	5	M	Larynx Trachea	C: 2 A: 8 T: 10	Eight in Africa (from 2007 to 2009) 38 in our center (since 2009)	Local cidofovir	6/11	Yes 2016–2017
4	2019	39	M	Nasopharynx Oropharynx	C: 0 A: 11 T: 11	2	Local cidofovir	6/11	No
5	2004	60	M	Larynx	C: 4 A: 14 T: 18	13 in another Belgian center	Local cidofovir	Not tested	Yes

Abbreviations: A, anatomic Derkay score; C, clinical Derkay score; F, female; HPV, human papilloma virus; M, male; T, total Derkay score.

2.1 | Patient 1

Of our five patients, this is the one with the most aggressive, most extensive (from the larynx to the lungs), and most heavily pretreated form of RRP. This female patient was diagnosed at the age of 3 and underwent more than 150 surgical procedures during her lifetime, with several adjuvant treatments. Parallel to papillomas, she suffers from multiple surgical complications such as laryngeal stenosis and currently requires a tracheostomy.

2.2 | Patient 2

This Rwandan patient, diagnosed with a juvenile form of laryngeal RRP at the age of 4, arrived in Belgium 18 years later, having already had more than 30 surgical procedures. After a first course of bevacizumab, he had to go back to Rwanda for work, and, despite an active RRP recurrence, stayed for almost 3 years without any treatment. Currently, he has an important laryngeal recurrence, and the treatment with bevacizumab has just been resumed.

2.3 | Patient 3

This Beninese patient is the youngest of our series. He was diagnosed with a laryngotracheal RRP at the age of 5 and underwent more than 40 surgical procedures. After an adjuvant treatment with cidofovir in loco combined with HPV vaccination, the disease was better controlled, and the patient went a few months without treatment. Bevacizumab was begun when he relapsed 1.5 years later. After the end of bevacizumab treatment, the patient was lost to follow-up because of the COVID-19 pandemic; we currently do not know if the disease is still in complete remission 1 year later.

2.4 | Patient 4

This patient was diagnosed at the age of 39 with a naso- and oropharyngeal form of RRP responsible for snoring. Given the poor evolution despite two surgical interventions combined with cidofovir in loco, bevacizumab was started a few months after diagnosis.

2.5 | Patient 5

This patient with multiple comorbidities (atrial fibrillation, Wolff-Parkinson-White syndrome, type 2 diabetes mellitus, postsmoking COPD, chronic alcoholism) is the oldest, diagnosed at the age of 60 with a laryngeal form of RRP. After a 16-year history of 13 surgical procedures combined with adjuvant cidofovir and HPV vaccination, the disease was still active. For this reason, bevacizumab was started.

2.6 | Patients' histories

At the beginning of treatment, the patients were aged from 17 to 76 years (median 35). Four of five patients had laryngeal papillomatosis, and one had a naso- and oropharyngeal form. Among the four patients with laryngeal papillomatosis, two also had tracheal involvement and one had lung spread. HPV 6/11 was identified in two patients, two had HPV of undetermined type, and one was not tested for HPV. One patient had a history of malignant transformation (squamous cell carcinoma in situ). Among the five patients, four had already received multiple surgical interventions (most often by CO_2 laser) and one was treated with bevacizumab soon after diagnosis. The median time between the last laser surgery and bevacizumab initiation was 7 weeks (ranging from 2 to 20). Four patients had received previous adjuvant cidofovir (local for four, intravenous for one); one also received adjuvant interferon, mitomycin C, and photodynamic therapy. Four had been vaccinated against HPV prior to initiating bevacizumab treatment.

3 | BEVACIZUMAB TREATMENT

All patients provided an informed consent for the use of off-label treatment and received bevacizumab 10 mg/kg every 3 weeks, based on the dosage most commonly used in previous published clinical cases and series. An operative panendoscopy under general anesthesia—with resection of papillomatous lesions if needed—was performed before treatment was initiated. Before each subsequent dose of bevacizumab was administered, an awake viodeolaryngotracheoscopy was made in office. An operative panendoscopy was repeated only if necessary—for example, in case of doubt concerning the persistence of lesions, in order to perform biopsies, or to better assess the subglottic region. CT scans were only performed for the patient with lung involvement. The discontinuation of bevacizumab was left to the discretion of the otorhinolaryngologist. The best response observed was classified as complete, partial, stable, or progressive. The efficacy was also assessed by the Derkay staging system, which quantifies the severity of the disease based on clinical criteria and involvement of anatomic structures.[18] The adverse events are reported according to CTCAE v5.0.

4 | RESULTS

Complete response was achieved in four patients after a median of 4.5 months, ranging from 2 to 6. In those, the treatment was stopped after a few months (median 20 cycles, ranging from 16 to 34). In three of those four cases, a recurrence of the disease led to resumption of treatment a few months later (median 8 months, ranging from 7 to 9). All these patients subsequently responded again after resumption of treatment. One patient was diagnosed with a pulmonary recurrence 12 months after discontinuing bevacizumab. A CT scan performed 3 months after its resumption showed regression of all lung lesions. One patient had to interrupt the treatment for administrative reasons (work abroad); during this interval, he received no treatment for RRP, and came back with an important recurrence after almost 3 years, whereupon he resumed treatment with bevacizumab. In the fifth case, a partial response was achieved, and the treatment could never be interrupted for more than 2 months. In all patients, the start of bevacizumab was rapidly followed by a drastic reduction in the number of surgeries, and therefore in general anesthesia. This evolution of the annual number of endoscopic procedures for each patient is presented in Figure 1.

Considering all patients, the average Derkay score before treatment was 15.4, ranging from 10 to 25. The average Derkay score was reassessed after 12 months and fell from 15.4 to 1.8, ranging from 0 to 4.

For three patients, the reduction in repeated surgical procedures was considered an improvement in general quality of life, as it allowed them to lead a more normal life and carry out certain projects. According to the clinical Derkay score, an improvement in respiratory-related quality of life was reported by three patients. There was no significant improvement in voice-related quality of life. This lack of improvement is probably due to the amount of scarring and synechia related to past surgeries; they cause stiffness of the larynx, preventing the proper vibration of the vocal cords.

For patient 1, the good control of the disease and a dramatic reduction in the frequency of surgical procedures allowed her to realize a desire for pregnancy. Since bevacizumab is contraindicated during pregnancy due to the risk of fetal malformations, and as the disease was

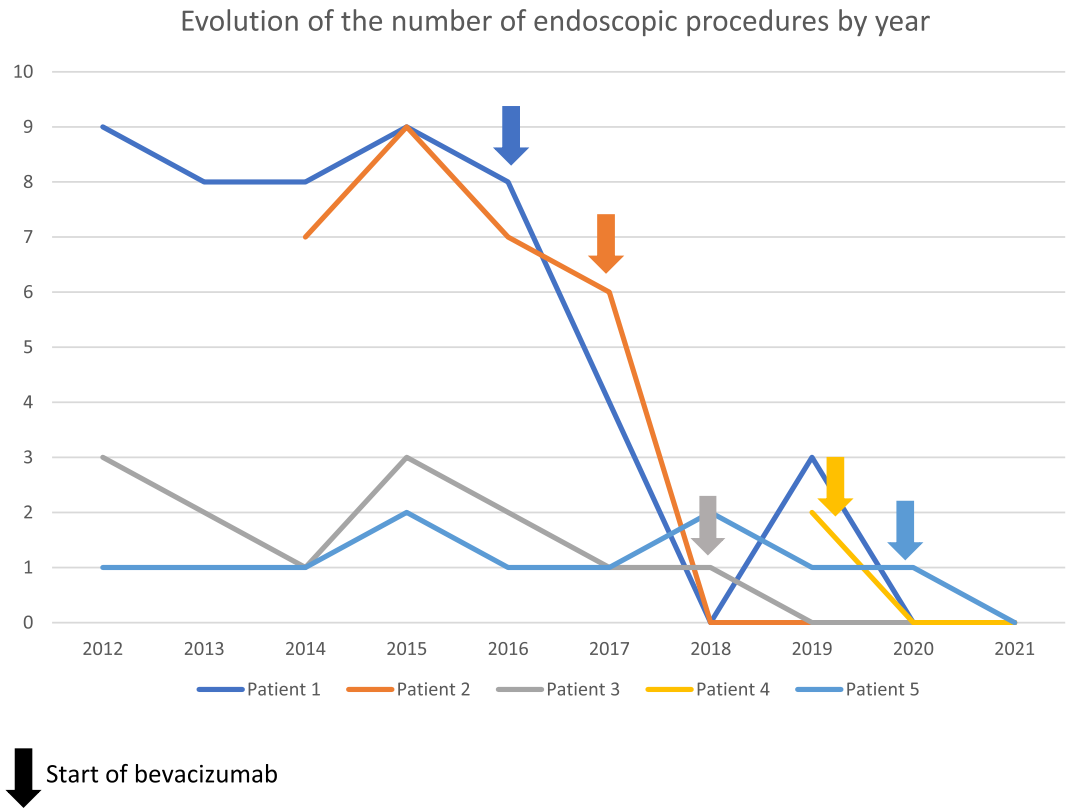

FIGURE 1 Evolution of the number of endoscopic procedures by year for the past 10 years (2012–2021) for each patient. [Color figure can be viewed at wileyonlinelibrary.com]

well controlled, bevacizumab was interrupted after 22 doses. The patient was instructed to wait 6 months before becoming pregnant, but 5 months later, her baby was already on the way. The beginning of the pregnancy went very well. The disease remained stable for a couple of months, but at 7 months of pregnancy a millimeter-size laryngeal lesion was noticed, and the biopsy confirmed a recurrence of the papillomatosis. At first (because of the pregnancy), a simple follow-up was proposed. When the pregnancy had come to term, the birth had to be induced because of preeclampsia, and the patient gave birth to a healthy baby boy without other complications. A CT scan was performed and showed that the papillomatosis had spread to the lungs. Thus, bevacizumab was resumed only 6 weeks after delivery, which unfortunately put an end to breastfeeding.

Overall tolerance was good. The reported adverse events were grade 1 proteinuria in four patients, grade 2 proteinuria in one patient, grade 2 hypertension in two patients, and grade 3 spontaneously reversible neutropenia in one patient. One patient developed a mild gravidic hypertension and proteinuria, and preeclampsia without severe features.

These adverse events were manageable. For proteinuria screening, a urinalysis was performed before each dose of bevacizumab was administered. In case of grade 1 proteinuria, the treatment was continued without other investigation. For the patient with grade 2 proteinuria (confirmed with a 24-h urine collection), bevacizumab was discontinued (but this grade 2 proteinuria appeared precisely 1 year after the start of bevacizumab, so at the time when we planned to stop the drug). A nephrology consultation was planned for 3 months later, at which time the proteinuria was still present but had returned to grade 1. No other explanation for this proteinuria was found. A 3-month follow-up visit with the nephrologist is planned. The grade 2 hypertension observed in two patients was easily controlled with a calcium antagonist (amlodipine) in one and a combination of calcium antagonist (amlodipine) and angiotensin-converting enzyme inhibitor (perindopril) in the other. Clinical efficacy and tolerance are summarized in Table 2.

5 | DISCUSSION

While there is no high-level evidence supporting the use of bevacizumab as an adjuvant treatment for RRP, some authors have published interesting data suggesting its effectiveness on papillomatous lesions.

TABLE 2 Summary of clinical efficacy and tolerance (as of June 23, 2022).

Patient	Date of bevacizumab initiation	Age at bevacizumab initiation	Best response	Time to achieve CR	Derkay score after 12 months of bevacizumab	Number of interventions in 12 months before 1st bevacizumab	Number of interventions in 12 months after 1st bevacizumab	Number of cycles received	Freedom from progression after treatment discontinuation	Bevacizumab-free interval	Adverse events
1	2017/09/07	26	CR	6 months	C: 4 A: 0 T: 4	8 for papillom. 0 for complic.	0 for papillom. 5 for complic.[a]	1st course: 21 2nd course: 22 3rd course: 7 (ongoing)	7 months 12 months	7 months 17 months	Grade 1 proteinuria Gravidic hypertension Gravidic proteinuria
2	2017/10/11	35	CR	2 months	C: 1 A: 0 T: 1	7	0	1st course: 19 2nd course: 2 (ongoing)	7 months	30 months	Grade 1 proteinuria
3	2018/12/21	17	CR	6 months	C: 0 A: 0 T: 0	2	0	34	Lost of follow-up since the end of bevacizumab (April 2021)	14 months (ongoing)	Grade 1 proteinuria Grade 3 neutropenia
4	2019/08/29	39	CR	3 months	C: 0 A: 0 T: 0	2	0	1st course: 16 2nd course: 17	8 months	9 months 1 month (ongoing)	Grade 2 proteinuria Grade 2 hypertension
5	2020/06/02	76	PR	/	C: 2 A: 2 T: 4	2	0	31 (ongoing)	/	/	Grade 1 proteinuria Grade 2 hypertension

Abbreviations: /, not applicable; A, anatomic Derkay score; C, clinical Derkay score; Complic., complications of repetitive surgeries; CR, complete response; Papillom., papillomatosis itself; PR, partial response; T, total Derkay score.

[a]Interventions for complications of repetitive surgeries in patient 1: posterior cordectomy, laryngeal dilatation and excision of laryngeal fibrous tissue, subtotal arytenoidectomy, right cordectomy, laryngeal microsurgery with laser vaporization for lifting of laryngeal synechia.

In 2005, Rahbar et al. reported the results of a retrospective study investigating the role of VEGF-A in the pathogenesis of RRP. They compared laryngeal biopsies from 12 children with a history of laryngeal RRP to samples from normal pediatric larynx obtained by autopsy. They found strong expression of VEGF-A mRNA in the squamous epithelium of papillomas of the 12 RRP patients and in none of the samples from the control cases. Similarly, strong expression of VEGFR-1 and VEGFR-2 was found in the endothelial cells of the underlying vessels in all 12 patients and in none of the control cases.[19]

In 2021, Verma et al. reported the results of a prospective cohort of 32 patients with RRP surgically treated from November 2016 to June 2019 and recruited in a single center in India. The systemic and tissue expression of VEGF-A were assessed by immunohistochemistry and ELISA assay for the 32 RRP patients as well as for control samples obtained from healthy peripheral tissue of laryngectomy specimens. The analyses showed that the serum and tissue expression of VEGF-A were higher among patients with RRP than in control samples ($p < 0.001$), especially in cases of severe disease or tracheobronchial involvement.[20]

In 2014, Ahn et al. used xenograft models (patient-derived papilloma tissue grafted into immunodeficient mice) to test the efficiency of bevacizumab in vivo. They observed a dramatic response with the administration of bevacizumab 5 mg/kg, 2 times per week for 3 weeks.[9]

In humans with RRP, bevacizumab was first used in loco. In 2011, Zeitels et al. were the first to report the efficacy and safety of low-dose sublesional injections of bevacizumab combined with KTP laser in a prospective open-label investigation including 20 adult patients with bilateral vocal fold papillomatosis.[21] Since then, other authors have shown good results with the use of intralesional bevacizumab for both adult- and juvenile-onset RRP.[22–24]

Since the use of local adjuvant bevacizumab was reported, several cases and small series of RRP patients treated by adjuvant systemic bevacizumab have been published.[25–37] To our knowledge, the biggest series to date is that of Tkaczuk et al. in 2020. They reported the cases of 14 patients with severe RRP, the majority with juvenile onset. For all these patients, the introduction of systemic bevacizumab reduced the need for surgical procedures and improved the quality of life, especially related to vocal and respiratory comfort.[38]

Our five cases combined with those from the literature support the use of systemic bevacizumab as an adjuvant treatment for severe RRP. However, clinical trials providing high-level evidence are lacking, and bevacizumab is still used in RRP as an off-label treatment. If most authors seem to agree on a dose of 10 mg/kg every 3 weeks, two parameters still need to be defined: when to begin and how long to continue the treatment?

To establish some official consensus for the use of systemic bevacizumab, a multidisciplinary panel of 70 experts from 12 different countries was created. It brought together physicians experienced in the use of systemic bevacizumab for RRP, from various departments such as otolaryngology, hemato-oncology, infectious diseases, pediatric surgery, family medicine, and epidemiology. They identified several criteria, encouraging the use of bevacizumab based on patient, disease, treatment center, and prior workup characteristics. Their conclusions were published by Sidell et al. in 2021. They agreed on several points. There is no age limit: both children and adults can receive bevacizumab. However, the treatment is contraindicated for pregnant and lactating women. The patients should agree to undergo several laryngo/bronchoscopies and provide informed consent for the off-label use of the drug. Frequency of surgical interventions, rather than disease longevity, is an important variable triggering the use of bevacizumab. Bulky and rapidly progressive disease as well as locations difficult to treat with standard surgery are also criteria supporting the use of bevacizumab. The treatment should be administered under the supervision of a trained physician in a specialized center, after a laboratory test comprising at least a normal complete blood count. No consensus was reached regarding a standard pretreatment radiologic workup, which should be undergone on a patient-by-patient basis. In any case, a good understanding of the extension and histologic characteristics—including HPV typing and evaluation for malignancy—is recommended.[39]

Standards for the duration of treatment are less clear. Some authors give a cycle of bevacizumab from time to time, whenever it is clinically indicated. Others give it every 3 weeks for a few months. For our patients, treatment was continued at the same 3-week interval and maintained for a few months after complete remission. In most clinical trials testing bevacizumab as adjuvant treatment for solid cancers, it has been administered for 12–15 months—for example, GOG-0218 in ovarian cancer, BEATRICE in triple-negative breast cancer, E1505 in nonsmall-cell lung cancer, and AVANT in colon cancer. Thus, although our timing is not based on any evidence from RRP, we currently tend to interrupt the treatment after 1 year. However, despite their very good clinical responses, all our patients relapsed after a few months of treatment interruption.[40–43] Therefore, it could be interesting to try a maintenance therapy every 2 or 3 months, in order to maintain remission. It would allow the patients to have fewer hospital contacts and a more normal life. Indeed, even without additional surgery, visiting the hospital every 3 weeks for endoscopy and bevacizumab treatment can disrupt daily life, especially for young patients. Moreover, even though the treatment was globally well-

tolerated, our two adult patients developed grade 2 hypertension, which can lead to long-term complications. Regarding patient 4, it is interesting to note that his blood pressure rapidly normalized during the interval without bevacizumab. All the patients also developed mild proteinuria, which rapidly normalized during bevacizumab-free intervals. We therefore think that a cycle every 2 or 3 months would have less effect on blood pressure and proteinuria. Prospective studies comparing different doses and timings would be interesting but are not easy to conduct, given the rarity of the disease.

Concerning tolerance of the treatment, adverse events reported in our series were concordant with the known safety profile of bevacizumab. However, we can wonder whether preeclampsia is or is not related to bevacizumab. As bevacizumab is contraindicated during pregnancy, little is known about a potential link between the two. As reported by Cross et al., bevacizumab can induce a preeclampsia-like syndrome in non-pregnant women.[44] It is therefore difficult to say if the gravidic hypertension and proteinuria were related to bevacizumab or to a real preeclampsia linked to placental dysfunction.

6 | CONCLUSIONS

Based on these observations and the published research, systemic bevacizumab seems to be an effective and safe option as adjuvant treatment for aggressive forms of RRP, both in children and adults. Randomized prospective studies are still needed to provide high-level evidence supporting its use, and the best way to use it (dose, frequency, and what to do after complete response).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Pubmed (https://pubmed.ncbi.nlm.nih.gov).

ETHICS STATEMENT

Each patient provided a written informed consent according to our ethics committee's requirements.

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