To report on the efficacy of rituximab (RTX) therapy in standard treatment–refractory, chronic Henoch-Schönlein purpura, a retrospective chart review of 3 pediatric patients treated with RTX for severe refractory chronic Henoch-Schönlein purpura was performed. All 3 patients responded to 1 or 2 courses of RTX without serious adverse events. (J Pediatr 2009;155:136-9)

Case Reports

Case 1
A 17-year-old white boy had diffuse, intermittent abdominal pain. He had hypertension, with hematuria and hypoalbuminemia (3.1 g/dL). Abdominal computed tomography revealed jejunal wall edema. On the eighth day, the patient had development of palpable purpura on his lower extremities and hematochezia. Over the next month, he was admitted to the hospital on 4 occasions for abdominal pain, hematochezia, and anemia (Table). Renal biopsy revealed proliferative glomerulonephritis with IgA deposits consistent with World Health Organization class III IgA nephropathy. The patient received several days of high-dose intravenous methylprednisolone, which improved his nausea, vomiting, purpura, and hematochezia. However, he did not tolerate steroid tapers, had development of steroid-induced hyperglycemia requiring insulin, and required repeated red blood cell transfusions. He received a cyclophosphamide infusion and high-dose methylprednisolone, but his condition worsened while receiving prednisone 1.2 mg/kg/d in between the thrice-weekly methylprednisolone infusions. The patient received 1000 mg RTX infusions twice 2 weeks apart, and he received mycophenolate mofetil 2 weeks after the initial RTX dose. His proteinuria improved, and his hematocrit rose from 15.7% to 35%, and within 3 weeks of his first RTX infusion, the purpura, fevers, and hematochezia completely resolved. A video capsule endoscopy before RTX revealed small intestinal ulcerations and active bleeding; the patient’s mucosa completely normalized in appearance within 1 month of RTX (Figure). He remains in remission 5 months after RTX on no immunomodulating medications.

Case 2
A 14-year-old white boy presented with a 1-month history of abdominal pain and palpable purpura on his abdomen and upper and lower extremities. He responded to high-dose methylprednisolone, but during a steroid taper, abdominal pain and rash returned, and he had severe headaches. Skin biopsy revealed a small-vessel neutrophilic vasculitis with IgA deposition, consistent with HSP. One month after diagnosis, the patient was readmitted for recurrent abdominal

H enoch-Schönlein purpura (HSP) is a small-vessel vasculitis that is characterized by nonthrombocytopenic purpura, abdominal pain, arthritis and arthralgia, and glomerulonephritis.1 Although usually self-limited, HSP can be severe and chronic, presenting with gastrointestinal hemorrhage and chronic renal insufficiency. Refractory HSP has most commonly been treated with corticosteroids;2 additional studies have reported the use of steroid-sparing therapeutics, including cyclosporine,3 intravenous immunoglobulin,4 azathioprine,5 cyclophosphamide,6 methotrexate,7 and mycophenolate mofetil.8 However, not all patients with chronic HSP will remit with these therapies. Because of the important role of B cells in HSP,9,10 rituximab (RTX), a therapeutic monoclonal antibody against the surface antigen CD20 expressed by B cells,11 appears to be an attractive intervention for patients with refractory HSP. In particular, immunoglobulin A (IgA) has been implicated in HSP in terms of deposition in the tissues, abnormal glycosylation patterns, and affinity for endothelial cells.12 Although RTX should not deplete terminally differentiated, immunoglobulin-secreting plasma cells, the benefit afforded by RTX’s depletion of B cells in other B cell–mediated disorders warrants its use in refractory HSP.13,14 We describe the safe and effective use of RTX in 3 patients with therapy-resistant severe chronic HSP.
pain and was found to have pancreatitis. The pancreatitis resolved with corticosteroids, but 6 weeks into his illness abdominal pain and rash recurred. These responded to pulse methylprednisolone. The patient remained off steroids for 16 months with intermittent flares (rash and arthralgias), but gross hematuria, lower extremity palpable purpura, edema, arthritis, and hypertension (167/78 mm Hg) eventually developed. At 1.5 years into the illness, the patient received 4 doses of RTX (375 mg/m²/dose) at weekly intervals. He received a steroid taper of 0.18 mg/kg/d to 0.02 mg/kg/d over the course of 4.5 months, and 33 months after RTX he remains symptom free and receives no immunomodulating medications.

Case 3
A previously healthy 10-year-old white girl had development of palpable purpura on her lower extremities and buttocks, as well as periarticular swelling and arthralgias. Severe abdominal pain developed 6 weeks after disease onset, and abdominal computed tomography showed bowel wall thickening; intravenous methylprednisolone therapy was initiated. Fulminant upper gastrointestinal bleeding ensued, resulting in hypovolemic shock, requiring massive fluid and red blood cell resuscitation and vasopressor therapy. A skin biopsy showed granular deposition of IgA and fibrin in superficial vessels, confirming HSP. Severe headaches commenced and a brain magnetic resonance angiogram (MRA) showed

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**Table.** Features of HSP and response to therapy in 3 patients treated with RTX

<table>
<thead>
<tr>
<th>Features/labs/therapy</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at diagnosis</td>
<td>17</td>
<td>14</td>
<td>10.5</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Palpable purpura</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>Yes, Class III</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum creatinine before RTX</td>
<td>0.7 mg/dL (Normal: 0.6-1.5 mg/dL)</td>
<td>1.0 mg/dL (Normal: 0.6-1.5 mg/dL)</td>
<td>Not available</td>
</tr>
<tr>
<td>Serum creatinine after RTX</td>
<td>1.1 mg/dL (Normal: 0.6-1.5 mg/dL)</td>
<td>0.8 mg/dL (Normal: 0.6-1.5 mg/dL)</td>
<td>Not available</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>Seizure</td>
<td>Headsaches</td>
<td>CNS vasculitis</td>
</tr>
<tr>
<td>Gl distress/bleed</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ESR (highest)</td>
<td>22 mm/hr (Normal: &lt;15 mm/hr)</td>
<td>33 mm/hr (Normal: &lt;15 mm/hr)</td>
<td>20 mm/hr (Normal: &lt;20 mm/hr)</td>
</tr>
<tr>
<td>Hct (lowest)</td>
<td>15.7 % (Normal: 39-54%)</td>
<td>38.1 % (Normal: 39-54%)</td>
<td>38.4% (Normal: 30-42%)</td>
</tr>
<tr>
<td>CD19+ lymphocytes before RTX</td>
<td>111/mm²</td>
<td>Not done</td>
<td>349/mm²</td>
</tr>
<tr>
<td>CD19+ lymphocytes after RTX</td>
<td>&lt;1 (&lt;6 indicates depletion)</td>
<td>Not done</td>
<td>-1 (&lt;6 indicates depletion)</td>
</tr>
<tr>
<td>Inadequate response to cyclophosphamide</td>
<td>Yes</td>
<td>Not prescribed</td>
<td>Yes</td>
</tr>
<tr>
<td>Inability to taper corticosteroids</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Time in remission as of November 2008</td>
<td>5 months</td>
<td>33 months</td>
<td>7 months</td>
</tr>
</tbody>
</table>

CNS, Central nervous system; GI, gastrointestinal; ESR, erythrocyte sedimentation rate; Hct, hematocrit.

**Figure.** **Left Panel,** Resolution of gastrointestinal bleeding after RTX therapy. A video capsule endoscopy revealed multiple bleeding, **center panel,** ulcers in the small bowel of case 1. **Right panel,** A follow-up video capsule endoscopy performed less than 1 month after RTX therapy revealed the lesions had completely healed.
irregularity of both middle cerebral arteries and the left anterior cerebral artery, suspicious for central nervous system vasculitis. Several days of high-dose methylprednisolone resulted in rapid resolution of abdominal pain and intestinal bleeding. A follow-up MRA performed 4 weeks later showed worsening of the involved vessels and new irregularities of the posterior cerebral arteries. Treatment with intravenous pulse cyclophosphamide therapy (750 mg/m^2 monthly) was commenced, and MRA performed 2 months later supported mild interval improvement of the cerebral vascular abnormalities. While corticosteroid was tapered, abdominal pain and purpura recurred, and severe back pain caused by compression fractures of thoracic vertebrae occurred. Because of the persistent central nervous system vasculitis despite cyclophosphamide therapy, the patient received 4 weekly infusions of RTX 375 mg/m^2, resulting in complete B-cell depletion (Table). MRA performed both 6 weeks and 12 months after RTX showed complete resolution of intracranial vascular abnormalities. Subsequently, cyclophosphamide treatment was discontinued, and azathioprine and dapsone were begun while corticosteroids were tapered. Azathioprine and dapsone were discontinued 14 months after disease onset. One month later, the patient had development of recurrent palpable purpura, soft tissue swelling, and abdominal pain after an upper respiratory infection. B cells had repopulated with an absolute B cell count of 349/mm^3. Treatment with azathioprine and dapsone was resumed, and RTX was given in 4 weekly infusions (375 mg/m^2). This resulted in rapid resolution of purpura, soft tissue swelling, and abdominal pain. The patient continues without disease symptoms 7 months after the second round of RTX.

**Discussion**

Several studies have reported the effectiveness of the combination of steroids and cyclophosphamide in the treatment of refractory HSP with severe nephritis. However, there have been no reports on the effectiveness of cyclophosphamide with gastrointestinal manifestations associated with HSP. Patient 1 received 1 infusion of cyclophosphamide, and his gastrointestinal symptoms continued to progress. Therefore it is unlikely that the use of this intervention contributed strongly to his improvement. In addition, patient 2 initially responded to steroids and later relapsed; however, his illness resolved rapidly with RTX in combination with a steroid taper. Patient 3’s illness persisted when on azathioprine and dapsone but resolved rapidly once RTX was begun. All 3 patients’ conditions improved rapidly after the use of RTX, with resolution of skin conditions, gastrointestinal symptoms, central nervous system status, and laboratory values, without RTX-related complications. This is consistent with the reported benefits of RTX in other forms of vasculitides and bespeaks of the importance of B lymphocytes in the pathogenesis of these disorders. B cells are important participants during the immune response (eg, antigen presentation and costimulation) and not simply destined to secrete potentially pathogenic antibodies; therefore therapeutic depletion or disruption of B cells holds promise for treating a variety of vasculitides. The response to RTX in the 3 patients presented herein warrants future studies in severe HSP refractory to traditional interventions.

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Reprint requests: Randy Q. Cron, Children’s Hospital of Alabama, CPP 210, 1600 7th Avenue South, Birmingham, AL 35233-1711 E-mail: rcrnon@peds.uab.edu.

**References**


In the 1950s, if a child with diarrhea was not infected with Salmonella, Shigella, or Vibrio cholerae, the cause would remain unknown. In this context, Neter reviewed mid-century knowledge of enteropathogenic Escherichia coli (EPEC).

Elegant studies by Varela, et al1 and Bray and Beavan in the 1940s1 (neither of which were cited in Neter’s review), introduced a definable diarrheagenic subset of E. coli, termed EPEC,3 which belonged to a limited number of serotypes. EPEC caused severe epidemics into the 1980’s in this country. Typical EPEC are defined by their clustered adherence to epithelial cells, in and their ability to induce cytoskeletal rearrangements in host cells. EPEC are fascinating phylogenetically: many distantly related EPEC contain similar suites of chromosomal and plasmid-borne virulence genes. Atypical EPEC (aEPEC) are also pathogens; some aEPEC are enterohemorrhagic E. coli (EHEC) that have lost Shiga toxin genes.4

It is ironic that as our understanding of EPEC biology has blossomed, the epidemiological and clinical importance of EPEC has been overshadowed by other diarrheagenic E. coli, including EHEC and aEPEC.4,5 However, except for EHEC O157:H7 (which has aEPEC characteristics), clinicians cannot easily identify diarrheagenic E. coli. Many diarrheal episodes remain undiagnosed even when stools are subjected to comprehensive evaluations. We are seeing genomic- and viromic-based nominations of many new candidate enteric pathogens. Investigators will be challenged to expeditiously confirm or refute the virulence of such agents with the rigor and curiosity of the investigators from the 1940’s and 1950’s.

References


