Why does Mycophenolate use only for kidney complications in Schonlein Henoch Syndrome? Case report

Maria Francesca Gicchino (francesca.gicchino@gmail.com)
Universita degli Studi della Campania Luigi Vanvitelli https://orcid.org/0000-0003-0329-6583
Dario Iafusco
Universita degli Studi della Campania Luigi Vanvitelli
Maria Maddalena Marrapodi
Universita degli Studi della Campania Luigi Vanvitelli
Rosa Melone
Universita degli Studi della Campania Luigi Vanvitelli
Giovanna Cuomo
Universita degli Studi della Campania Luigi Vanvitelli
Angela Zanfardino
Universita degli Studi della Campania Luigi Vanvitelli
Emanuele Miraglia del Giudice
Universita degli Studi della Campania Luigi Vanvitelli
Alma Nunzia Olivieri
Universita degli Studi della Campania Luigi Vanvitelli

Case Report

Keywords: Shonlein Henoch Syndrome, Purpura, Mycophenolate Mofetile

Posted Date: March 11th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-16795/v1

TITLE PAGE

Why does Mycophenolate use only for kidney complications in Schonlein Henoch Syndrome? Case report

Maria Francesca Gicchino, Dario Iafusco, Maria Maddalena Marrapodi, Rosa Melone, Giovanna Cuomo*, Angela Zanfardino, Emanuele Miraglia del Giudice, Alma Nunzia Olivieri

Department of Woman, Child and General and Specialized Surgery , Naples, Italy
***Department of Precision Medicine, Naples, Italy**

University of Campania "Luigi Vanvitelli" , Naples, Italy

Corresponding Author: Maria Francesca Gicchino

Via De Crecchio, 4 – 80138 Naples – Italy

almanunzia.olivieri@unicampania.it

Phone + 39 081 5665428
Mobile + 39 339 8826510
Fax + 39 081 5665430

Words count 1,720

Why does Mycophenolate use only for kidney complications in Schonlein Henoch Syndrome?

Maria Francesca Gicchino, Dario Iafusco, Maria Maddalena Marrapodi, Rosa Melone, Giovanna Cuomo*, Angela Zanfardino, Emanuele Miraglia del Giudice, Alma Nunzia Olivieri

Background:

Henoch Schonlein purpura (HSP) is an acute small vessel vasculitis. It is the most common vasculitis in children. Although the cause is unknown, IgA seems to play a central role in the pathogenesis of Henoch Schonlein purpura. The major clinical features include a palpable purpuric rash on the lower extremities, abdominal pain or renal involvement, and arthritis. Cutaneous manifestations are the essential elements in the diagnosis of Henoch Schonlein purpura. The palpable purpura is characteristically 2 to 10mm in diameter and is usually present on the lower extremities. There are no specific diagnostic tests available for diagnosing this condition. Laboratory studies are useful to exclude other conditions that may mimic Henoch Schonlein purpura. In majority of the cases, the disease is self-limited. Relapsing can occur, in particular during the first year of the disease. There is no consensus on a specific treatment. Corticosteroids are effective in rapid resolution of renal and abdominal manifestations. Immunosuppressive drugs, such as Mycophenolate Mofetil may be a better treatment choice in case of renal involvement.

Case report: We report a case of a 14 years old girl affected from recurrent Henoch Schonlein Purpura. From the age of nine years patient presented three episodes of purpura with gastrointestinal involvement, in particular hematemesis, abdominal pain and diarrhoea. Each episode was treated with high doses of corticosteroids (methylprednisolone in vein or prednisone per os). Patient came to our Department during the third episode of Purpura. In consideration of the recurrence of the Henoch Schonlein Purpura and the gastrointestinal involvement we decided to start Mycophenolate Mofetil treatment. Patient's conditions improved thanks to Mycophenolate Mofetil treatment.

Conclusion:.In our case of recurrent HSP Mycophenolate Mofetil treatment has been very effective, avoiding the adverse events of a prolonged steroid treatment. This experience teaches us that immunosuppressive agents may be very useful to induce and maintain remission not only in renal involvement, but in all cases of persistence, recurrence or complicated forms of Henoch Schonlein purpura in children.

Key Words
Shonlein Henoch Syndrome, Purpura, Mycophenolate Mofetile

1.Background

Henoch–Schönlein purpura (HSP) is the most common systemic vasculitis in children[1]. The majority of those patients are under 10 years old [2]. Annual incidence of HSP in children is estimated to be 15/100,000 cases.[3] The proportion of males and females in children is close to 2:1.[4] Diagnostic criteria were published by the European League against Rheumatism and the Pediatric Rheumatology European Society which include palpable purpura (obligatory) in combination with at least one of other manifestations (gastrointestinal involvement, immunoglobulin A deposition in biopsy, arthritis or arthralgia, and renal involvement) [5] Table1. Clinical manifestations are: palpable purpura (96%), arthralgia/arthritis (64%), abdominal pain (66%), gastrointestinal bleeding (28%), renal involvement (39%), subcutaneous edema (42%), orchitis (5%). Patient may present rarely severe pulmonary hemorrhage(1%), or cerebral vasculitis(2%).[6] Purpuric rashes are the most typical manifestation. The prognosis of HSP is generally good, but recurrence is common among children (recurrence rate, 2.7%–66.2%)[7]. Significant morbidity and mortality are associated with gastrointestinal tract lesions and nephritis. The development of major indicators of renal disease within the first six months after onset or the recurrence of numerous exacerbations associated with nephropathy suggests a poor prognosis for renal function. Additional poor prognosis factors are decreased factor XIII activity, hypertension, renal failure at onset.[8] Treatment is supportive, with maintenance of good hydration, and with control of pain with analgesics. However, the efficacy and safety of the therapy with steroids and immunosuppressants in treating HSP are still controversial.[9] [10] Corticosteroids are useful in children with gastrointestinal disease, hemorrhage, severe orchitis, kidney involvement. Immunosuppressive treatment of HSP nephritis is used in patients with severe kidney involvement (nephrotic range proteinuria and/or progressive renal impairment).[11] There are few data in literature regarding treatment of recurrent HSP without kidney involvement. We report the successful use of MMF in a patient affected from recurrent HSP with gastrointestinal involvement.

Criterion	Definition
Purpura (mandatory)	Purpura palpable or petechiae, with lower limb predominance, not related to thrombocytopenia
At last 1 of the following	
Abdominal pain	Diffuse, acute coliky pain. May due to intussusception and gastrointestinal bleeding
Histopathology	Leucocytoclastic vasculitis with IgA deposit, or proliferative glomerulonephritis with IgA deposit
Arthritis or arthralgia	Arthritis. Acute joint swelling or pain with limitation on motion. Arthralgia. Acute joint pain without joint swelling or limitation on motion
Renal involvement	Proteinuria>0.3g/24hr; spot urine albumin to creatinine ratio>30mmol/mg, or 2+on dipstick Hematuria, red cell casts. Urine sediment showing >5 red cells per high power field or red cells casts

Table n 1 :Modified from Ozen S. et al. The EULAR/PRINTO/PRES criteria for HSP, Ann Rheum Dis 2010 [5]

2.Case presentation

Episode 1 (2012). At the age of 8 years, after a febrile pharyngitis treated with Amoxicilline-clavulanic, patient presented pain in her lower limbs with difficulty walking and purpuric lesions to the limbs. During hospitalization in a local hospital she was treated with oral prednisone, 2mg/kg/die. She was discharged for disappearance of symptoms after 1 week with diagnosis of suspected vasculitis and therapy with prednisone (2mg/kg/die) for 10 days.

Episode 2 (2015) After three years of good conditions, patient presented hematemesis and purpuric lesions so she was hospitalized again. Laboratory tests: complete blood count, kidney and liver parameters, electrolytes and coagulation test, urinalysis, faecal calprotectin, antinuclear antibodies (ANA) celiac screening, virological testing , throat swab were unremarkable. Abdomen ultrasound, was normal. Methylprednisolone iv (30mg/kg/die) was started, then oral prednisone (25mg twice a day) was prescribed. She was discharged after 1 month with Schonlein Henoch Vasculitis diagnosis. Oral prednisone was suspended after 10 days. After 15 days from prednisone suspension patient

presented relapse with hematemesis and purpuric lesions, so she was hospitalized again. She underwent esophagogastroduodenoscopy (EGDS) that was negative. Resigned with corticosteroids therapy (oral prednisone 25 mg twice a day) for about a month. Patient presented good condition for three years.

Episode 3 (March 2018), at the age of 15 years after an episode of pharyngitis appearance of diffuse rash, so she was admitted in hospital again with diagnosis of vasculitis and corticosteroids treatment for 10 days (oral prednisone 25 mg twice a day) was prescribed. As she suspended corticosteroids treatment she presented again purpuric lesions on the lower limbs. So she was admitted to the hospitalized again. During hospitalization oral prednisone (50 mg/die) was started again. In this occasion patient presented the first episode of hypertension. Laboratory tests (complete blood count, kidney and liver parameters, coagulations tests, ANA, rheumatoid factor, inflammatory indices, immunoglobulins, complement C3 and C4, thyroid hormone, urinalysis, virological examinations), throat swab were negative. Skin biopsy was suggestive of leukocytoclastic vasculitis, with IgA deposition, typical of HSP.HSP was confirmed and oral steroids (prednisone 25 mg twice a day, gradually reduced) was prescribed. As she reduced oral prednisone, hematemesis, epistasis and diarrhea came back again. Patient was evaluated to emergency and she underwent to abdomen ultrasonography revealing bowel wall thickening. Steroids were prescribed again by increasing the dosage (prednisone 25 mg twice a day). For the persistence of abdominal pain and maculo papular lesions on the limbs, trunk, abdomen patient came to our observation for the first time. Secondary amenorrhea since four months was referred. On the examination she presented acne on the face and back. No arthritis was detected. Her blood tests were unremarkable for: complete blood count, liver and kidney function, erythrocyte sedimentation rate (ERS), C-reactive protein (CRP), Antinuclear antibodies (ANA), extractable nuclear antigens (ENA), Anti neuthophil Cytoplasmic antibodies (ANCA), rheumatoid factor (RF), anti-double stranded DNA (dsDNA) immunoglobulins, complement C3 and C4, thyroid hormone, sexual hormones, blood cortisol . Factor XIII activity was reduced (65%, normal value > 75%). Urinalysis was normal. Throat swab was negative. Abdomen

and pelvic ultrasound was in the norm. Both gynecological and ophthalmologic evaluation were normal. So therapy with oral prednisone 25 mg in the morning and 20 mg in the evening was prescribed. After few days she presented new purpuric lesions at the knees and feet, so therapy with mycophenolate mofetil (750mg twice a day) was added to oral prednisone (40 mg/die) due to the recurrent nature of her symptoms and the lack of a sustained response to glucocorticoids. She performed mycophenolate mofetil therapy for 8 months, with complete regression of vasculitic lesions. Patient had sustained remission for 12 months off corticosteroids and MMF. At the last follow up visit patient was in good conditions, she did not present rash or vasculitic lesions and laboratory test was normal.

Discussion

We described a case of a patient affected from recurrent HSP with gastrointestinal involvement who had been successfully treated with MMF .The treatment of HSP is controversial. In clinical practice management of HSP includes supportive care, symptomatic therapy and, in some cases, immunosuppressive treatment. Arthritis/arthralgia usually responds well to non-steroidal anti-inflammatory drugs (NSAIDs). Specific therapy is limited to the care of the most important complications including especially kidney involvement. Steroids have been the first-line therapeutic regimen for many kinds of glomerulo-nephritis over years[10]. Corticosteroids are useful in children with gastrointestinal disease, hemorrhage, severe orchitis, kidney involvement. Early GCS treatment have included shorter duration of abdominal pain, decreased risk of intussusception and decreased risk of surgical intervention.[12,13] . Immunosuppressive treatment of HSP nephritis is used in patients with severe kidney involvement (nephrotic range proteinuria and/or progressive renal impairment)[10]. Recent studies in children with HSP nephritis and nephrotic syndrome suggest a potential benefit of cyclosporine A (CsA) or Mycofenolate Mofetil in achieving remission of proteinuria .[14,15]

In our case the patient presented a severe gastrointestinal involvement responsive to high and prolonged doses of corticosteroids with all the side effects that this therapy entailed so we decided to

start an immunosuppressive treatment with Mycophenolate Mofetil. This drug is very effectiveness in many rheumatological diseases also in paediatric age such as lupus erythematous systemic and vasculitis .[16] In table 2 are described all the side effects of all immunosuppressant drugs used for treatment of vasculitis. Adverse effects of MMF include diarrhoea, bone marrow suppression, opportunistic infections; these side effects are rare and less severe than the secondary consequence of prolonged corticosteroid therapy. In particular, in children, a long exposure to corticosteroid could induce also growth impairment. MMF seems to be an effective steroid-sparing medications, allowing steroid-dipendent patients to be tapered off steroids. No official guidelines are available for treatment duration.

Table 2 [17]

	Cyclophosphamide (CYC)	Azathioprine	Mycophenolate mofetil (MMF)	Ciclosporin	Methotrexate	Corticosteroids
Dose	2-3 mg/kg once a day PO 2-3 months; 0.5-1.0g/m2 IV monthly with mesna to prevent cystitis	0.5-2.5 mg/kg once a day PO for 1 yr or more	(600 mg/m2 twice a day)	3-5 mg/kg/day PO in 2 divided doses	10-15 mg/m2/week PO or SC (single dose)	Prednisolone 1–2 mg/Kg PO Prednisone 1-2 mg/Kg PO MetilPrednisolone 30 mg/kg max 1g EV
Side Effects	Leucopenia ; haemorrhagic cystitis; leukaemia, lymphoma, transitional cell carcinoma of bladder	GI toxicity; hepatotoxicity; no increase in malignancy in adults with RA; no conclusive data for cancer risk in children	Bone marrow suppression; severe diarrhoae; pulmonary fibrosis	Renal impairment, hypertension, hepatotoxicity, tremor, gingival hyperplasia, hypertricosis, lymphoma	Bone marrow suppression and interstitial pneumonitis (risk with folic acid), reversibile elevation of transaminases, hepatic fibrosis	Growth Imparment Diabetes Hypertension Dyselectrolites Oedema Hypokaliemia Osteopenia Musles atrophy

Side effects and dose of main drugs used for the chronic treatment of vasculitis

Conclusions

This anecdotal case demonstrates that MMF may be beneficial for the induction and maintenance of remission of recurrent HSP with gastrointestinal involvement representing steroid sparing medications. Our patient had no adverse events associated with MMF therapy. Immunosuppressant agents should be useful for the induction and maintenance of remission of all persistence, recurrence

or complicated cases of HSP in children. Further randomized controlled trials comparing the different treatments for these patients are needed.

List of abbreviations

SHP: Shonlein Henoch Purpura
MMF: Mycophenolate Mofetile
ANA: Anti Nuclear Antibodies
ANCA: Anti Neutrophil Cytoplasmic Antibodies
ENA: Extractable Nuclear Antigens
RF: Rheumatoid Factor
DS-DNA: Anti Duble Stranded-DNA
EGDS: Esophagogastroduodenoscopy
ESR: Erythrocyte Sedimentation Rate
CRP: C-Reactive Protein
NSAIDs: non Steroidal Anti Inflammatory Drugs
GCS: Glucocorticosteroids
CSA: Cyclosporine A

Ethical approval: Not applicable
Consent to participate: Not applicable

Consent for publication Written consent for publication has been obtained from the parents of the patient

Availability of data and material: Not applicable
Competing Interests: Authors declare no potential competing interests with respect to research authorship and/or publication of this article
Funding: Not applicable

Authors' contributions: GMFconceived the paper, involvement in the diagnosis and follow up of patient, analyzed and interpreted the patient data and first writer of paper; MMM, MR and ZA diagnosis and management of patient, analyzed and interpreted the patient data, writer of paper and revision of bibliography; ID, CG, MDGE and OAN supervision of the medical procedures, including the decision of the use of MMF, writer of paper.
All authors read and approved the final manuscript.

Acknowledgements
We are grateful to Prof Ranjith Kothalawalage for the English revision of this paper

234 **Reference**

[1] Hetland LE, Susrud KS, Lindahl KH, et al. Henoch-Schonlein purpura: a literature review. Acta Derm Venereol 2017; 97: 1160–6.

[2] He X, Yu C, Zhao P, et al The genetics of Henoch–Schonlein purpura: a systematic review and meta-analysis. Rheumatol Int 2013; 33(6): 1387–1395.

[3] Kang Y, Park JS. Differences in clinical manifestations and outcomes between adult and child patients with Henoch-Schonlein purpura. J Korean Med Sci 2014; 29: 198–203.

[4] Reid-Adam J. Henoch-Schonlein purpura. Pediatr Rev 2014; 35: 447–9.

[5] Ozen, S., Pistorio, A., Iusan, S. M. et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Annals of the Rheumatic Diseases, 2010; 69(5): 798–806.

[6] Cassidy JT, Petty RE, Laxer RM et al. Textbook of pediatric rheumatology Ed Elsevier 2011

[7] Wei-Te L, Po-Li T, Szu-Hung C, et al. Incidence and risk factors for recurrent Henoch-Schönlein purpura in children from a 16-year nationwide database. Pediatr Rheumatol Online J. 2018; 16: 25.

[8] Rao S, Singhal V, Kamath N. Henoch Schonlein Purpura: classification and management- an update. Karnataka Paediatric Journal 2012; 26, No 1

[9] Fotis L, Tuttle PV, Baszis KW, et al Azathioprine therapy for steroid resistant Henoch Schonlein Purpura: A report of 6 cases Pediatric Rheumatology 2016;14:37

[10] Jiaxing T, Yi T, Zhengxia Z, et al The efficacy and safety of immunosuppressive agents plus steroids compared with steroids alone in the treatment of Henoch–Schonlein purpura nephritis: A meta-analysis. Int Urology and Nephrology 2019. Doi 10.1007/s11255-019-02092-7

[11] Hetland E, Kjærsti Sørensen S, Hein Lindahl K and Bygum A Henoch-schonlein purpura: a literature review. Liv Acta Derm Venereal 2017; 97: 1160-1166

[12] Fangfang Y, Zhaohui B, Yingying L et al. A good response to glucocorticoid for Henoch–Schönlein purpura with abdominal pain and gastrointestinal bleeding in an adult A care case report Medicine 2020; 99(1): e18602.

[13] Weiss PF, Klink AJ, Localio R *et al*. Corticosteroids may improve clinical outcomes during hospitalization for Henoch-Schönlein purpura. Pediatrics 2010; 126: 674– 681.

[14] Park JM, Won SC, Shin JI *et al*. Cyclosporin A therapy for Henoch-Schönlein nephritis with nephrotic range proteinuria. Pediatr. Nephrol. 2011; 26: 411– 417.

[15] Hackl, A., Becker, J. U., Körner, et al. Mycophenolate mofetil following glucocorticoid treatment in Henoch-Schönlein purpura nephritis: the role of early initiation and therapeutic drug monitoring. Pediatric Nephrology, 2017; 33(4), 619–629

[16] Rodriguez-Smith J, Brunner HI Update on the treatment and outcome of systemic lupus erythematous in children. Curr Opin Rheumatol. 2019; 31(5): 464-470.

[17] Foster H and Brogan P Paediatric Rheumatology –Ed OSH Paediatrics 2012

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- checklist.pdf
- checklist.pdf