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Recent Advances in the Treatment of Henoch-Schönlein Purpura

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Abstract

Henoch-Schönlein purpura (HSP) is a self-limited benign disease, which is characterized by inflammation of blood vessels. Clinically, it presents with abdomen pain, joint pain and palpable rashes mainly in the lower limbs and buttocks. As the disease progresses, it affects the renal system, causing hematuria and proteinuria. Pathophysiologically, there is deposition of IgA and C3 complement complexes. Diagnosis of HSP is made by investigations such as ESR, CRP, urine analysis and microscopy, serum electrolytes and creatinine, blood urea and urine protein creatinine ratio. Renal biopsy is also done in cases with severe renal involvement. HSP is treated with corticosteroid therapy conventionally along with symptomatic treatment with non-steroidal anti-inflammatory drugs for the joint pain and abdominal pain. With the advancements in the treatment, recently advanced therapy is being studied and tried in order not only to treat HSP, but also to induce long-term remission, and prevent recurrences. With the many adverse effects of steroid therapy, other drugs which have a direct effect on the pathophysiology of the illness have proved to be effective in the treatment of HSP as well as in maintaining remission. Dapsone, Azathioprine, Mycophenolate Mofetil and Rituximab are few of the drugs, and plasmapheresis is a recent therapy, which have been effectively used in complicated cases of HSP. The recent advances in the treatment of HSP have been helpful in preventing the side effects caused by the conventional steroid therapy, steroid dependency and recurrences.

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Introduction

Henoch-Schönlein purpura (HSP) is a condition in which inflammation of the blood vessels occurs, hence, it is known as vasculitis. It is characterized by the deposition of IgA antibody, so called as IgA vasculitis. This disease involves, apart from the blood vessels, the skin, mucous membranes and sometimes other organs, most commonly the kidneys [1]. This disease presents with a triad of symptoms: palpable purpura (small, raised areas of bleeding underneath the skin), joint pain and pain abdomen. The rash is usually purplish to red, palpable and typically on the buttocks and lower limbs [2]. When there is kidney involvement, hematuria and proteinuria are noted, but this usually goes unnoticed; in a small number of cases, the kidney involvement progresses to chronic kidney disease. HSP may also cause intussusceptions causing bowel obstruction and often follows an infection, such as a throat infection, chickenpox, measles and hepatitis. Exposure to cold temperatures, certain food items, insect bites or certain medications are few other triggers [3]. HSP can affect anyone but is common in children between the age of 2-6 years [4]. The pathophysiology of HSP is the deposition of IgA and Complement 3 (C3) in the arterioles, venules and capillaries [1]. The exact cause of this is unknown. It has been suspected that the abnormalities of the IgA1 molecule may be the cause for the deposition of IgA antibodies in the blood vessels, either due to increased production of IgA1 in the digestive tract or bone marrow or due to decreased removal of the IgA1 molecule from the circulation [5, 6]. The cause of the initial inflammation of the blood vessels is not clear. The inappropriate response of the immune system to certain triggers has been thought to be the cause of the inflammation [7].

Early morbidity in the disease is due to the involvement of the gastrointestinal tract and the late morbidity is due to the renal involvement. HSP is a benign, self-limited disease which ideally requires no treatment. In the absence of kidney disease, the illness lasts for approximately one month [4]. The cases which present with very severe symptoms or nephritis have commonly been noticed to have recurrences. For symptomatic relief and to reduce the duration and severity of the skin manifestations as well as the gastrointestinal and joint symptoms, glucocorticoids have been seen to be effective [8]. Successful use of steroids is seen in patients with reduced oral intake due to the gastrointestinal symptoms, patients who have difficulty in ambulation, or those with a painful rash [7]. Though steroids are commonly used in the day to day clinical practice, there are no evidence-based recommendations for their use in HSP and their effect on the final outcome, particularly the renal disease remains unaltered [9]. The objective of this review is to emphasise on the uses of new drugs, which have recently been found out to play an effective role in the treatment of HSP. This new treatment deletes the flaws, which are seen in the presently used steroid therapy.

Investigations and diagnosis

On investigation, HSP is presented with elevated ESR or CRP, elevated IgA and elevated platelet levels. This can be used to distinguish it from conditions like idiopathic thrombocytopenic purpura and thrombotin thrombocytopenic purpura, in which, the cause of the purpura is the reduced platelet levels [1]. With the involvement of the kidneys, there may be elevated blood urea and serum creatinine levels. Urine analysis is another investigation necessary in a case of HSP [5]. In the case of significant renal involvement with hematuria, proteinuria or hypertension; or severe abdominal pain, further investigations would be required like urine protein creatinine ratio, blood urea, serum creatinine, serum electrolytes, serum albumin, and urine microscopy. If the diagnosis is unclear and to identify the potential complications, further investigations required are blood and urine culture, abdominal imaging; anti-nuclear antibody, anti-dsDNA, ANCA and C3/C4 [6]. Biopsy of the skin may also be helpful in differentiating HSP from vasculitis due to cryoglobulinemia and immunofluorescence, which demonstrates IgA and C3 in the blood vessel wall [3]. Renal biopsy shows IgA deposition in the glomeruli and crescentic

changes. In order to determine the progression of the renal disease, the number of glomerular crescents has been attributed to be an important factor of prognosis [8].

Treatments

HSP is a self-limited illness. Treatment is only supportive and symptomatic and is focused on controlling the severity of the illness rather than its treatment per se. Subcutaneous edema can be managed with complete rest and by elevating the edematous area. For mild pain, nonsteroidal anti-inflammatory drugs like ibuprofen 10 mg/kg three times a day or naproxen 10 mg/kg two times a day can be given if not otherwise contraindicated. A paracetamol may be added. The risk of Reye's syndrome should also be kept in mind [9].

Corticosteroids

For moderate pain, steroids like oral Prednisolone 1-2 mg/kg/day or intravenous Methylprednisolone 0.8-1.6 mg/kg/day till symptoms persist are recommended followed by appropriate weaning regimen once the symptoms resolve. It should be noted that the steroids do not have an impact on the renal complications of HSP [10]. A study was performed in order to examine the prevention and treatment of kidney disease and Prednisone was given for 14-28 days to children with HSP. The result showed that the difference in the risk of persistent kidney disease at 6 months and 12 months was found to be not significant when compared with any supportive or placebo treatment. When Cyclophosphamide was given to children with HSP, compared with supportive treatment, it was noted that the difference was not significant in view of the development of the risk of persistent renal complications. The same result was obtained with Cyclosporin as compared to Methylprednisolone [11]. Large prospective studies on the treatment of HSP are lacking and there is no evidence to support the view that steroids can prevent or treat kidney disease. Steroids may be nevertheless considered in conditions like persistent nephritic syndrome, more than 50% crescentic changes in the glomeruli, severe gastrointestinal haemorrhage, severe soft tissue oedema, severe scrotal oedema, intrapulmonary haemorrhage and neurological system involvement [12]. The long-term prognosis of HSP is based on the severity of renal involvement. Therapy may be beneficial to patients with HSP-related renal dysfunction. Prophylaxis for kidney disease in HSP is not recommended yet. Overt HSP is treated with Methylprednisolone pulse therapy, Prednisone and other immunosuppressive medications. A regimen consisting Prednisone 1-2 mg/kg/day orally for 7 days is recommended. In cases of HSP with renal involvement, anti-hypertensive medications may be indicated [11, 12]. The following protocols have shown favourable results in patients with severe HSP as reported by Iqbal et al. [13]. Induction with 250-750 mg of intravenous (IV) Methylprednisolone daily for 3-7 days plus Cyclophosphamide 100-200 mg/d administered orally (PO); maintenance with Prednisone 100-200 mg PO every other day plus Cyclophosphamide 100-200 mg/d PO 30-75 days; tapering of Prednisone by approximately 25 mg/month (with the Cyclophosphamide dose remaining constant) and discontinuance of treatment after at least 6 months by abruptly discontinuing Cyclophosphamide and tapering Prednisone completely. The skin lesions in HSP can alter the patient's quality of life significantly as they are very crippling. Steroids have shown to be ineffective or they have only a transient effect on skin lesions [13].

Recent advances in the treatment of HSP

Intravenous or oral steroids in addition to other drugs like Azathioprine, Cyclosporine, Cyclophosphamide, Dipyridamole, high dose intravenous immunoglobulin G Danazol, and fish oil are other treatment regimens. In dermatology, guidelines for prescribing Azathioprine have been established [14]. In regard to the use of intravenous Immunoglobulin G, factor XIII administration, antioxidant vitamin E, and fish oil; no convincing studies have yet been conducted to treat HSP. Before using Azathioprine, Mycophenolate mofetil, and urokinase, their use has to be advocated consistently. In a randomised clinical trial, in which Cyclosporine and Methylprednisolone pulsed were used in HSP with nephritis, Cyclosporine was found to be superior and had fewer complications [14]. In

a study, in which 12 patients had HSP with severe nephritis, Methylprednisolone 30m/kg/day for 3 days followed by oral steroids 2 mg/kg/day for a period of 2 months, Cyclophosphamide 2mg/kg/day for 2 months and Dipyridamole 5mg/kg/day for 6 months showed positive results and these patients responded well to this therapy [14]. Intravenous immunoglobulin G infusion was given in patients with isolated intestinal HSP with massive gastrointestinal haemorrhage and was found to be responsive. It was also used in a complicated case of HSP with brain haemorrhage, but the use of this treatment still needs to be validated [13].

Dapsone

Dapsone is an antileprotic drug which is used in a variety of dermatological conditions. Dapsone has been found to have a special value in conditions in which there is an accumulation of neutrophils as seen in leukocytoclastic vasculitis and HSP is an example for the same [15]. It acts by inhibiting the synthesis of IgA and IgG antibodies as well as by inhibiting the production of prostaglandin D2. It also has been found to inhibit the interactions between IgA antibodies and neutrophils [16]. Dapsone has been observed to control the cutaneous vasculitis rather than curing it. Dapsone can be used as a reasonable alternative to steroids as steroids may mask the features of more ominous intestinal disease [15]. Several researchers found Dapsone to be effective in the treatment of HSP associated with purpuras and arthralgias. There was a positive effect of Dapsone on the skin rash, but few cases relapsed and few developed nephritis [13, 15]. Therefore, the use of Dapsone has to be reevaluated in children with HSP; although it can control cutaneous vasculitis, it has no positive effect on relapse or nephritis, which determines the prognosis of HSP [16]. Dapsone may suppress the synthesis of IgG and IgA antibodies and also suppress the generation of toxic free radicals from neutrophils; nevertheless, the study could not show a beneficial effect of Dapsone on renal disease, which might be a limitation of this drug [15].

Azathioprine

HSP progresses to a chronic form of the disease in a small percentage of children, which often requires prolonged corticosteroid therapy [17]. For refractory cases of HSP, disease modifying anti-rheumatic drugs (DMARDs) or biologics have been reported to be effective. Azathioprine, a DMARD has recently been found effective in cases of HSP nephritis and adult cutaneous leukocytoclastic vasculitis [17]. A study of six patients with HSP relapse without kidney disease, treated with Azathioprine has been reported. The relapse occurred in spite of using corticosteroids. All six patients were successfully treated with Azathioprine and tapered off of corticosteroids. Azathioprine was given for the duration of 7-21 months and no adverse effects were reported [18]. Therefore, Azathioprine has been found to be effective in controlling prolonged relapsing symptoms of HSP so that corticosteroids can be discontinued earlier. The combination of Azathioprine with corticosteroids or other agents was used in cases of HSP nephritis and was reported to improve the clinical course of the nephritis, though randomised controlled trials are needed for the same [18]. As per the opinion of experts, the use of Colchicine or Dapsone is favoured as the first line of treatment for conditions with cutaneous leukocytoclastic vasculitis [17]. Many experts are recommending Azathioprine as the second line of treatment for cutaneous leukocytoclastic vasculitis. Elevation of liver enzymes, nausea, anorexia, vomiting and the theoretical report of increased risk of malignancy are the main concerning facts about the use of Azathioprine [17]. The levels of thiopurine-S-methyltransferase (TPMT), whose genetic variation has been related to the observed bone marrow toxicity, is required to adjust the dosage of Azathioprine to reduce the risk of infections and the idiosyncratic arrest of granulocyte maturation [19]. In this case series of using Azathioprine as the second line of treatment, monitoring of complete blood count and complete metabolic panel were performed to evaluate blood dyscrasias or liver toxicity and no adverse events were reported [18]. Azathioprine has been reported as an effective steroid-sparing medication so that all patients dependent on steroids can be successfully tapered off and discontinued from steroids. In this case

series, the optimal duration of Azathioprine was not established and thus, an official guideline was not available for the duration of treatment with Azathioprine [19]. Hence, once the symptoms are controlled, the therapy can be discontinued empirically after remission of the disease has been achieved for 6-15 months [19]. To summarize, from this case series, it has been demonstrated that Azathioprine improves the control of symptoms, has steroid sparing effect and induces remission in cases of recalcitrant HSP without the involvement of the renal system. No patient showed any adverse reaction to this therapy. The comparison of different therapeutic options for such patients is yet to be done by randomized controlled trials.

Rituximab

In severe refractory chronic HSP, Rituximab has been observed to be an effective and successful treatment. Rituximab is an immunomodulator, which causes B cell depletion and reduces the number of circulating IgA as well as inhibits the production of IgA, thereby, targeting the basic pathogenesis of HSP [20]. In a case study, the patient was given a single therapy with only two doses of Rituximab 1000 mg at the interval of two weeks. After three months, there were no rashes and only scars remained, no hematuria or proteinuria, and improvement in the CRP level, serum creatinine, and albumin levels were observed. After 22 months, sustained and complete remission of the kidney and skin manifestations was seen in the patient [21]. Hence, it showed that Rituximab is an important advancement in the treatment of HSP. It is given when treatment of HSP with steroids and Cyclophosphamide or Azathioprine has failed. The patient was not given any previous immunosuppressive treatment or steroids and responded well to a single therapy of Rituximab without any clinical signs of nephritis or vasculitis even after 22 months [22]. The benefits of rituximab in different forms of vasculitis and autoimmune diseases, and in three children with refractory chronic HSP as a standard treatment have been reported in many clinical trials, although the biological functions of Rituximab and its incapacity to deplete differentiated immunoglobulin-secreting plasma cells have not been clearly defined [23]. It can be concluded that inhibition of IgA production would be a positive step towards the treatment of HSP and Rituximab may be efficacious in treating cases of HSP with severe renal complications.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive agent. The use of MMF in many of the autoimmune diseases is increasing and now it is beginning to be successfully used in the treatment of HSP in cases with failure of response to corticosteroid therapy [24]. MMF acts by suppressing the proliferation of lymphocytes and by decreasing the production of antibody in renal diseases. ANCA–associated vasculitis develops due to the adhesion of leukocytes to the endothelial cells. The active metabolite of MMF, that is mycophenolatic acid, has been found to significantly inhibit the endothelial adhesion of leukocytes [25]. It was reported by Han et al. [25] that the disease activity was effectively controlled by MMF and renal function improved in Chinese patients with MPO-ANCA–associated vasculitis. When MMF was used in a few patients with HSP, it was observed that during the first week of treatment, HSP symptoms disappeared and at the end of the therapy as well as after its discontinuation, complete remission was seen in all patients [26]. Hence, by this trial, it was reported that MMF appeared to be a safe and effective drug for maintaining the remission in patients with HSP. The MMF is used in patients who are unresponsive to steroids, show side effects of steroid therapy and have steroid dependency in which case there may be relapses when the steroid doses are tapered. MMF is given in a dose of 30 mg/kg/day for a period of 3-4 weeks. The symptoms of HSP disappeared during the first week of therapy with MMF, which was effective in maintenance of remission in patients with HSP [26]. MMF has fewer side effects compared to other immunosuppressive agents and has anti-fibrotic and anti-proliferative effects. It has been recently considered to be of value in the treatment of complicated HSP and has shown beneficial effects in treating immunologically mediated renal diseases [27]. It can be concluded

that MMF proved to be a beneficial and alternative drug in treating complicated cases of HSP. In order to confirm the effects of MMF, it would be necessary to carry multi-centric trials with long-term follow-up.

Plasmapheresis

To delay the progression of kidney disease, Plasmapheresis may be effective. Plasmapheresis is used in cases which have progressive renal disease in spite of being on steroid and immunosuppressive therapy [28]. In a case series, it was demonstrated that adult patients with severe HSP treated with Plasmapheresis along with steroids showed positive outcomes. In children with IgA nephropathy and severe HSP treated with only plasma exchange without any immunosuppressive therapy showed good recovery, as reported by Shenoy et al. [28] in an uncontrolled study. In rapidly progressive HSP and nephritis, Plasmapheresis has been reported to be of use. Plasmapheresis is to be started early in the disease onset, about 2 weeks of onset of renal disease. The course of the renal disease is almost parallel to the circulating antibody titers. The patients who do not have kidney disease with HSP do not show these autoantibodies. Plasmapheresis may be effective in the removal of circulating antibody complexes or complexes which are already deposited in the mesangium [28]. Plasmapheresis is indicated in adult patients with HSP nephritis, and better be instituted early in the disease, especially in resistant cases [27]. Plasmapheresis should be started in patients who show deterioration of the renal disease in spite of being on steroid and/or immunosuppressive therapy. Severe bowel ischemia may be treated with surgery. In cases with severe kidney disease which are resistant to medical treatment, kidney transplantation can be indicated [29]. Evaluation of renal system manifestations should be continued in all patients for up to 6 months after presentation even if the urine analysis results are normal. In these cases, urine analysis and blood pressure monitoring should be done regularly. After the initial course of Prednisone, an additional course of Prednisone usually has no effect [29]. Long-term hemodialysis should be instituted until a kidney is available for transplantation when terminal renal failure develops. Mesangial deposits of IgA are common in the graft, but they rarely lead to clinical manifestations of recurrent glomerulonephritis [6, 28]. Children who are presented with renal manifestations in the acute phase and continue to have hematuria or proteinuria have to be examined every 3-6 months because hypertension or renal failure can develop up to 10 years after the onset of the disease [30].

Conclusions

Henoch-Schönlein Purpura is a self-limited illness. Treatment is given in order to stop the illness from progressing to severity and to prevent its long-term complications. Though the newer drugs require more studies and trials, their proven efficacy as per the presently available studies and trials, gives us the motivation towards the use of these drugs frequently during the day to day practice. In this review, the newly advanced drugs with their effects on HSP and the long-term efficacy have been discussed based on the previous trials and research outcomes. Multi-centric trials with close long term follow up are yet necessary to confirm the effectiveness of these drugs in HSP.

Conflict of interest

There is no conflict of interest.

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