Hong Kong J. Dermatol. Venereol. (2014) **22**, 169-173

Original Article

Hydroxyurea in the treatment of severe psoriasis: a retrospective review from Singapore

用羥基脲治療銀屑病：來自新加坡的回顧性分析

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Introduction: Hydroxyurea is a third-line systemic agent for the treatment of psoriasis in Singapore. We aimed to evaluate the therapeutic efficacy and safety of hydroxyurea. ***Methods:*** This was a retrospective review of all psoriasis patients started on hydroxyurea at a tertiary dermatology referral centre in the National Skin Centre, Singapore from 2004-2011. ***Results:*** Forty-seven patients were included. The mean body surface area (BSA) before starting hydroxyurea was 48% (2-80%). The best mean BSA achieved was 16.5% (4-60%). Clinical improvement was reported by physicians in 32% (n=15) of the patients and no improvement in 68% (n=32) of patients. From the patient's perspective; 4% (n=2) reported an excellent effect and 32% (n=15) good effect but 42% (n=20) had no effect and 21% (n=10) had worsening of their psoriasis. The adverse effects were minimal: 34% (n=16) no adverse effects; 53% (n=25) macrocytosis and mild megaloblastic anaemia; 8.5% (n=4) thrombocytopaenia; 6% (n=3) leucopaenia and 6% (n=3) cutaneous reactions. ***Conclusion:*** Our study suggests that hydroxyurea is relatively safe and effective in some patients and can be considered as a useful alternative for those who are unable to continue other systemic agents due to adverse events or cost.

簡介：在新加坡 ，羥基脲是治療銀屑病的第三線系統性藥物。我們的目的是評估羥基脲的療效和安全性。**方法**：這一個研究，回顧了所有從二零零四到二零一一年，在新加坡一間三級皮膚病轉介中心（全國皮膚中心）的銀屑病患者使用羥基脲的情況。**結果**：有四十七個患者包括在內，在使用羥基脲前平均體表面積爲 48%（2-80%）。16.5%（4-60%）達到了最佳的平均體表面積。醫師報告有 32% 的患者，其臨床症狀有改善（15 例），無改善的有 68%（32 例）。從患者的角度來看； 4%（2 例）有極好的效果， 32%（15 例）效果良好，但 42%（20 例）沒有影響，而 21%

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（10 例）更惡化了。不良反應甚微：34%（16 例）無不良影響；53%（25 例）有大紅細胞症和輕度巨幼紅細胞性貧血；8.5%（4 例）有血小板減少症；6%（3 例）有白細球減少症和 6%（3 例）有皮膚反應。**結論：**我們的研究發現，在部分患者，羥基脲是相對安全和有效的，並且可以被視爲在那些由於不良反應或成本過高而不能繼續使用其他全身性藥物的一個有用替代品。

Keywords: Hydroxyurea, management, psoriasis

關鍵詞：羥基脲、管理、銀屑病

Introduction

Psoriasis is a chronic disease, influenced genetically and environmentally and driven immunologically, affecting 1-3% of the world's overall population.[1] There are various agents available for the treatment of extensive chronic plaque psoriasis, from topical treatment, phototherapy to oral systemic medications. In the current era, newer treatments such as biologics are being used as well.[2] However, despite the availability of these treatments, the management of psoriasis remains a challenge. The treatment of choice is often determined by the efficacy, availability, affordability, safety and ease of administration.

Hydroxyurea is one of the third-line systemic agents that is considered at the National Skin Centre, Singapore in cases of psoriasis that are too extensive or refractory to topical therapy, phototherapy and other systemic agents such as methotrexate, acitretin and cyclosporin. It is also considered to be a useful alternative to those who are unable to continue with other systemic agents due to contraindications, adverse events or cost.

Hydroxyurea has been known to be effective in the treatment of psoriasis for more than 40 years and is postulated to work by reducing the replication of DNA within the basal cell of the epidermis.[3,4] The clinical response rate varies from 45% to 63% in patients with extensive chronic plaque psoriasis.[5-7] We aimed to evaluate the therapeutic efficacy and safety of hydroxyurea in our centre.

Methods

All patients with psoriasis started on hydroxyurea at the National Skin Centre from 2004 to 2011 were included in this study. The list of psoriasis patients started on hydroxyurea was obtained from the pharmacy records. A retrospective review of these patients' electronic medical records was done collecting data on demographics, prior treatment and indications for change over to hydroxyurea. The data was collected as part of a clinical audit at our centre.

An objective improvement was measured according to body surface area (BSA) of involvement. The evaluation of therapeutic response was done by assessing the BSA of involvement before and after starting hydroxyurea for at least three months or the best BSA achieved before stopping hydroxyurea. Subjective improvement was measured according to the global assessment by the physicians (improvement or no improvement) and the patients (excellent effect, good effect, no effect or worsening of psoriasis). The total duration of hydroxyurea therapy and adverse effects to hydroxyurea were recorded.

At our centre, the starting dose of hydroxyurea was 500 mg twice a day and the dose increment was at 500 mg per month. The dose range is 1 to 2 g per day. Hydroxyurea was withheld if the total white count was less than $2.5x10^9$/L, platelet count less than $100x10^9$/L or the patient had severe anaemia.

Results

Forty-seven patients were included. The mean age was 53.7 years and the male: female ratio was 3.3. The ethnic mix was 83% (n=39) Chinese, 6% (n=3) Malay, 9% (n=4) Indian and 2% (n=1) other races. The previous treatments used in these cases prior to switching to hydroxyurea and the indications for changing to hydroxyurea are shown in Table 1.

The mean duration these patients were on hydroxyurea was 19 months (3-84 months). The majority of patients, 87% (n=41), were started on a dose of 500 mg twice a day. However, only 26% (n=13) received a dosage increments of 500 mg per month. Most patients (96%, n=45) were on the correct dose (range 1 to 2 g per day, average 1 g per day). The mean duration of treatment required before these patients noted an improvement in their BSA was 3.5 months (0.25-15 months). The mean duration these patients on hydroxyurea without needing to change to other systemic therapies was 19 months (0.5 to 84 months).

The mean BSA before starting hydroxyurea was 48% (2-80%). The mean BSA before stopping hydroxyurea was 34% (1-80%). Seven patients continued hydroxyurea and to date, the best mean BSA achieved was 16.5% (4-60%) (Table 2). Out of the 40 patients who stopped hydroxyurea, the majority of patients (35%, n=14) had switched to topical treatment followed by 22.5% (n=9) methotrexate, 17.5% (n=7) cyclosporin, 10% (n=4) phototherapy, 7.5% (n=3) acitretin and 7.5% (n=3) biologic treatment.

Physicians reported a clinical improvement in 32% (n=15) of the patients and no improvement in

Table 1. Prior treatment & Indications for change over to hydroxyurea

Therapy	Drugs	No. of patients	Indications to stop	No. of patients (%)
Systemic	Methotrexate	40 (85%)	Liver abnormalities	23 (58%)
			Poor response	14 (35%)
			Nausea	3 (7%)
	Acitretin	20 (43%)	Poor response	9 (45%)
			Liver abnormalities	4 (20%)
			Cheilitis	3 (15%)
			Alopecia	2 (10%)
			Hyperlipidaemia	1 (5%)
			Cost	1 (5%)
	Cyclosporin	17 (36%)	Poor response	5 (30%)
			Renal impairment	5 (30%)
			Cost	4 (23%)
			Hypertension	3 (17%)
Biologics	Alefacept	4 (8%)	Poor response	4 (100%)
Phototherapy	NBUVB/PUVA	16 (34%)	Poor response	11 (69%)
			Time constraint	5 (31%)
Topicals	Steroids, coal tar, vitamin D analogues	47 (100%)	Poor response	47 (100%)

68% (n=32) of patients. From the patient's perspective, 4% (n=2) reported excellent effect and 32% (n=15) good effect but 42% (n=20) no effect and 21% (n=10) worsening of their psoriasis (Table 2).

The adverse effects were minimal with 34% (n=16) had no adverse effects, 53% (n=25) macrocytosis and mild megaloblastic anaemia, 8.5% (n=4) thrombocytopaenia, 6% (n=3) leukopaenia, 6% (n=3) cutaneous reactions and none had leg ulcers or hepatotoxicity (Table 3).

Discussions

The efficacy of hydroxyurea in psoriasis is usually seen within six to eight weeks of treatment.[5] In our patients, the improvement in their BSA was slightly delayed to 3.5 months (0.25 to 15 months). The longer duration taken in our patients to improve may be due to the varying definition of therapeutic response with different grading systems in different studies. Although the majority of patients (87%, n=41) were started on 500 mg twice daily, only 26% (n=13) received an increment dose of 500 mg per month. Hence, different treatment regimens with different rates of dosage increment may delay the rate of improvement.

The mean BSA before starting hydroxyurea was 48% (2-80%). The mean BSA before stopping hydroxyurea was 34% (1-80%) and the best mean BSA achieved was 16.5% (4-60%). In total, there was only 14% and at best 31.5% improvement overall. The physicians reported clinical improvement in 32% (n=15) of the patients and from the patient's perspective; 36% (n=17) reported good to excellent effect. The clinical

Table 2. Evaluation of therapeutic response

Characteristics	Data
Mean duration on hydroxyurea without needing to change to other systemic treatments	19 (3-84 months)
Mean BSA pre-hydroxyurea	48% (2-80%)
Mean BSA post-hydroxyurea	34% (1-80%)
Best mean BSA achieved	16.5% (4-60%)
Mean duration on hydroxyurea noted improvement in BSA	3.5 (0.25-15 months)
Global assessment	
Patient	
Excellent	2 (4%)
Good	15 (32%)
No effect	20 (42%)
Worsening	10 (21%)
Physician	
Clinical improvement	15 (32%)
No improvement	32 (68%)
No. of patients continued on hydroxyurea (to date)	7 (15%)

BSA=body surface area

Table 3. Adverse effects

Adverse effects	No. of patients	No. of patients needing to stop treatment	Comments
None	16 (34%)		
Macrocytosis and megaloblastic anaemia	25 (53%)	2	10 g/dL (NR*: 12-16 g/dL)
Thrombocytopaenia	4 (8.5%)	3	$100x10^3/\mu L$ (NR*: $140-440x10^3/\mu L$)
Leukopaenia	3 (6%)	2	WCC $<3x10^3/\mu L$ (NR*: $4-10x10^3/\mu L$)
Cutaneous reactions	3 (6%)	3	2 patients with skin pigmentation 1 patient with nail pigmentation
Total	47 (100%)	10 (21%)	

*NR: Normal range

response rate from the physicians' and patients' perspectives was lower than other reports (45-63%).[5-7] The possible reasons may be due to the recalcitrant nature of disease in our patients as all of them would have been tried on other systemic therapies before switching to hydroxyurea. The exact comparison in terms of BSA between other studies was not possible as most other authors had used PASI or other objective grading systems for the assessment of its efficacy. To date, seven patients are continuing on hydroxyurea as their psoriasis was adequately controlled although not completely cleared.

Hydroxyurea is a relatively safe treatment. In our study, 34% (n=16) had no adverse effects and there was no case of liver abnormality. The main adverse effect was myelosuppression: seven patients (15%) had to stop treatment and the myelosuppression was reversible without the need of blood transfusion. As with most studies, the myelosuppression was usually unremarkable and reversible on dose adjustments or stopping hydroxyurea.[7] Skin and nail pigmentation was noted in three patients (6%) and the treatment was stopped. This is a common side effect reported in 59% of patients and is usually reversible as seen in our patients.[5,8] None of our patients developed unusual complications such as dermatomyositis, oral ulcers or leg swelling.

In conclusion, our study suggests that hydroxyurea is effective in some patients, although slow-acting and can be considered as a useful alternative in those who are unable to continue other systemic agents due to adverse events or cost.[9,10] It is a relatively safe systemic treatment for our local population with minimal adverse effects. In the era of biologics, unfortunately because of cost, many patients who have failed standard systemic therapies are unable to afford long-term treatment with biologics. Hence, hydroxyurea remains a useful long-term alternative in view of its safety profile and relatively lower cost.

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