REVIEW ARTICLE

Role of Hydroxyurea in Psoriasis - A Review

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Summary:

Most of the patients of psoriasis have a chronic course with the need for continuous control of disease activity. Patients with moderate-to-severe disease generally require phototherapy, photo-chamotherapy or systemic agents (e.g. cyclosporine, methotrexate, oral retinoids, fumaric acid esters) to control their disease adequately. In general these therapeutic modalities have proven to be highly effective in the treatment of psoriasis. However, potentially serious toxicity can limit their long term use. In this respect, hydroxyurea compares favourably with methotrexate which has a potential for producing irreversible hepatic damage and cyclosporine A with its potential for dose-related nephrotoxicity. Hydroxyurea, a hydroxylated molecule of urea is commonly used to treat chronic myelogeneous leukemia and polycythemia vera. Recent studies suggest it as an alternative to methotrexate in moderate-to-severe psoriasis.

Key words: Hydroxyurea, psoriasis, efficacy of hydroxyurea.

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Introduction:

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. The most characteristic lesions consist of red, scaly, sharply demarcated, indurated plaques, present particularly over extensor surfaces and scalp.[1] Psoriasis is universal in occurrence. Epidemiological studies from around the world have estimated the prevalence of psoriasis to be anywhere from 0.6 to 4.8%.[2] According to another published report its prevalence in different population varies from 0.1 to 11.8%.[3]

Psoriasis is a chronic skin disease that may require lifelong intermittent treatment. Treatment usually starts with topical measures such as local corticosteroids, calcipotriol, dithranol/anthralin/cignolin or tar. It is assumed that about 30 % of patients have at least moderate disease, often requiring systemic treatment in addition to topical treatment. Patients with moderate to severe disease generally require phototherapy (e.g. narrowband ultraviolet B radiation), photo chemotherapy (oral psoralen plus ultraviolet A radiation) or systemic agents (e.g. Cyclosporine, methotrexate, oral retinoids, fumaric acid esters) to control their disease adequately. In general, these therapeutic modalities have proven to be highly effective in the treatment of psoriasis but have potentially serious toxicities with long-term use. There is no standard therapeutic approach for patients with moderate to severe psoriasis, the benefits and risks of phototherapy, photo chemotherapy and systemic therapy must be weighed carefully for each patient, and treatment should be individualized accordingly.[4] National Psoriasis Foundation (USA) Benchmark Survey found that systemic therapies widely used for psoriasis before 2003 have not fully met most patients' needs and less than 40 percent of psoriatic patients are very satisfied with any of the current therapies eg., acitretin, cyclosporine, methotrexate or PUVA.[5] As most of the new developments (biologics) only target single steps in a complex cascade of

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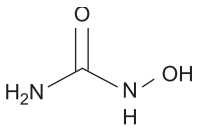
inflammatory immune-mechanisms, some are only partially sufficient. Further developments of classical anti-psoriatics or the discovery of new indications of non-dermatological old agents also can contribute to the enormous number of new products.[6]

In dermatology, hydroxyurea is used chiefly for the treatment of psoriasis. Efficacy has been demonstrated in plaque, pustular and erythrodermic forms.[7] In the three largest case series of patient with psoriasis treated with hydroxyurea, the reported satisfactory response rates have been ranged from 45 to 80%. Since the mid 1950s, methotrexate has become the gold standard by which other systemic psoriasis medications are measured.[8] Compared with methotrexate, it has the virtue of being a less frequent cause of anorexia, nausea and hepatoxicity.[1]

Background:

Hydroxyurea is a hydroxamic acid. It has the empirical formula $CH_4N_20_2$ and is a water-soluble, colorless, crystalline solid. Hydroxyurea was first synthesized in Germany in the 1869s by Dressler and Stein. Its efficacy in cancer therapy was reported in 1960. Kormeili et a1. demonstrated the drug's ability to induce leucopenia and anemia in animals. Today this chemotherapeutic agent is principally used to treat patients with chronic myelogenous leukemia.[9] The haematological side-effects of leukopenia and megaloblastic anaemia were noted in 1928. In 1960, retardation of growth in a number of malignant tumours in animals was noted and subsequent investigations established its value in the treatment of human chronic myeloid leukaemia. The favourable response of severe psoriasis to hydroxyurea was first reported by Leavell and Yarbro and subsequent reports have been made by Stein et al. and Kormeili et al.[10,11,9] Kipnis et al. suggests that hydroxyurea is an effective long-term treatment for psoriasis that is refractory to conventional topical therapy and that the incidence of serious adverse effects compares favourably with other cytotoxic drugs.[12]

Chemical Structure:



Pharmacology of Hydroxyurea:

Hydroxyurea may be administered orally, topically, and parentally.[13,14] Hydroxyurea is well-absorbed orally with peak plasma levels occurring at 1 or 2 hours. The onset of action is fairly rapid with tissue effects noted by 5 hours, peaked in 8 hours, and persisting for 20 hours. The half-life of the drug is 5.5 hours.[13] Roenigk and Maibach stated that after ingestion, hydroxyurea distributes in appreciable concentrations to tissues as well as to cerebrospinal fluid and breast milk.[15] The actual metabolism of the drug is unclear, although it may be metabolized to aceto-hydroxamic acid. Overall, 80% of the drug is excreted by the kidneys.[13] Hydroxyurea appears to have few significant drug interaction, with the exception of co-administration with other myelo-suppressive agents and cytarabin. Whitney and James stated that use of such agent with hydroxurea may lead to additive bone marrow toxicity.[7] Doses range from 1 to 1.5g/day taken in divided doses. The usual dose is 20 to 30mg/kg daily.[13]

Basic concept of pathogenesis of psoriasis:

In psoriatic epidermis, keratinocytes proliferate and mature rapidly so that terminal differentiation, normally occurring in granular keratinocytes and then squamous corneocytes, is incomplete. Hence, squamous keratinocytes aberrantly retain intact nuclei (parakeratosis) and release few extracellular lipids that normally cement adhesions of corneocytes. Accordingly, poorly adherent stratum corneum is formed and this results in the characteristic scale or flakes of psoriasis lesions. The epidermis of the mature lesion manifests markedly increased (approximately 10-fold) keratinocyte hyperproliferation extending to the lower suprabasal layers. Epidermal mass is increased three to five times, and there are many more mitoses observed frequently above the basal layer. The proliferative cell population is approximately doubled in psoriasis, whereas the cell cycle is more than 8 times shorter (36 vs. 311 hours) and daily production of keratinocytes in psoriatic lesions is approximately 28 times greater than that in normal epidermis.[3]

In the normal epidermis, basal keratinocytes divide approximately every 13 days, with the majority of this time spent in the G1 phase of the cell cycle. The maturation and subsequent shedding of these cells takes approximately 26 days. In contrast, the cell cycle of hyperproliferating psoriatic keratinocytes is shortened to approximately 1·5 days, while the maturation and shedding occur within 4 days. About 10 percent of basal keratinocytes are cycling in normal skin, whereas this value rises to 100 percent in lesional psoriatic skin. There is marked but not necessarily uniform loss of the granular layer with overlying compaction of the stratum corneum and parakeratosis, increased numbers of CD8+

T cells, and accumulation of neutrophils in the stratum corneum (Munro's micro abscesses).[15]

Theories to explain the relationship between the keratinocyte abnormalities and immune activation of psoriasis: Although the pathogenesis of psoriasis is not completely understood, it is likely that activated T lymphocytes and keratinocytes play a role in triggering and/or perpetuating the disease. There are two primary theories explaining the relationship between the keratinocyte abnormalities and immune activation. The first theory proposes that the primary defect arises in keratinocytes. Under this hypothesis, the defective epidermal keratinocytes are directly activated by physical, chemical, or ultraviolet injury (Koebner phenomena). These increase the synthesis and release of cytokines and result in an antigen-independent activation of T lymphocytes. The second theory suggests that the psoriasis is fundamentally a disease of the immune system and that abnormal keratinocyte proliferation and differentiation are a consequence of abnormal immune activity. According to this theory, persistent T-lymphocyte stimulation can be mediated through antigens or superantigens, or through autoimmunity. Keratinocyte hyperproliferation is stimulated by cytokines released from both T lymphocytes and keratinocytes. Previous studies have shown that psoriasiform epidermal hyperproliferation, perturbed keratinization, and inflammation occur in transgenic mice by suprabasal overexpression of integrins that are normally expressed in basal layer keratinocytes. This finding suggests that epidermal keratinocytes play an important role in the development of psoriasiform tissue reactions. Keratinocytes produce IL-6, IL-8, transforming growth factor -á (TGF-á), TGF-b, and amphiregulin. TGF-á and amphiregulin both stimulate hyperproliferation of keratinocytes and are, along with TGF-b, ligands for IL-1 and epidermal growth factor receptor (EGF-R), the expression of which is increased in psoriasis. IL-8 stimulates proliferation of keratinocytes and is also a chemoattractant for neutrophils and certain cells. Supernatants of psoriatic lesional, but not normal keratinocytes, can activate purified CD4+ T cells, emphasizing that they are capable of propagating skin inflammation. It is widely accepted that keratinocytes form a major cellular constituent of the skin immune system (SIS), in particular of the skin's innate immune defense. [3]

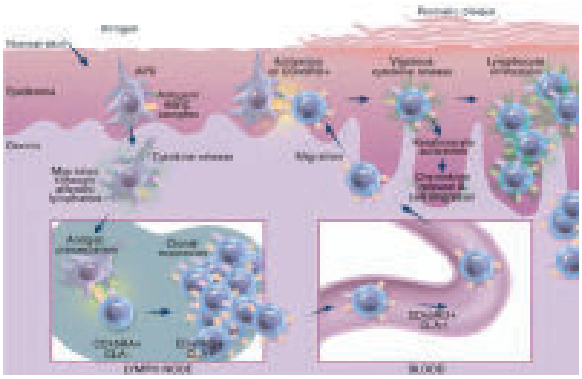


Fig.-1: *Generation of a T-cell response in the skin*

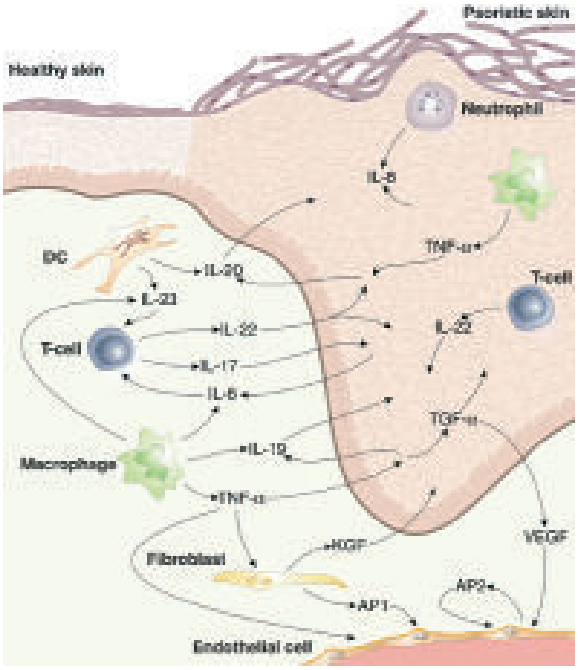


Fig.-2: *Various cell populations and their mediators are responsible for the 'keratinocyte response' stage of pathogenesis of psoriasis.*

Mechanism of action:

Hydroxyurea effects DNA synthesis, DNA repair, and gene regulation. The primary mechanism of action is through inhibition of ribonucleotide reductase, a rate-limiting enzyme in DNA synthesis. This enzyme catalyzes the reductive conversion of ribonucleotides to deoxy-ribonucleotides, which are integral to DNA synthesis. Another important feature of this drug is its action as a radiation sensitizer. Hydroxyurea may also

affect gene expression directly by causing hypomethylation of fetal hemoglobin gene leading to fetal hemoglobin induction, normalization of psoriatic skin by the induction of differentiation, and induction of other genes.[13] Hydroxyurea is most active in cells with high proliferative index. It is preferentially concentrated within leukocytes.[7]

Hydroxyurea profoundly influences the ribonucleotide reductase enzyme system within the cell. This enzyme catalyzes the conversion of ribonucleotides to deoxyribonucleotides and consists of two separate subunits, M_1 and M_2. M_2 is an iron-containing polypeptide and, unlike M_1, is present in varying cytosolic concentrations that depend on the cell cycle phase. Enzyme activity probably depends on cellular M_2 levels. Hydroxyurea binds to the M_2 protein and inactivates it. The non-heme component is believed to contribute. Cells in the synthesis phase of the cell cycle are killed selectively and proportionally depending on the concentration of hydroxyurea.[14]

Leavell and Yarbro suggested that hydroxyurea might inhibit DNA polymerase; other investigators disagree. Hydroxyurea also seems to play an inhibitory role in pyrimidine synthesis. Authors noted that thymidine or deoxyuridine incorporation into DNA was blocked by hydroxyurea but that protein synthesis was unimpeded.[10]

Hematologic changes are prominent in patients who receive this drug and may contribute to its alleviation of psoriasis. Jeffry believe that the megaloblastic changes undergone by red corpuscles influence the course of the disease. These authors hypothesize that conformational alterations of the cellular membrane, prohibit the blood cell from easily traversing the capillaries which denies the basal cell layer -the oxygen needed, to continue in a hyperproliferative mode. [14] Stein et al. in their study of pustular psoriasis believed that the number of circulating polymorphonuclear leukocytes were reduced and resulted in a suppression of pustule formation. Aberrant neutrophil chemotaxis has been shown in patients treated with hydroxyurea. [11]

The specific effects of this drug on epidermal cells have not been well studied. Kipnis et al. administered 7 gm of hydroxyurea to a patient with psoriasis. Subsequent lesional biopsy specimens demonstrated damaged cells in the epidermis with eosinophilic cytoplasm and pyknotic nuclei.[12] Kennedy et a1. have noted hydropic degeneration of the basal layer in patients treated for chronic myelogenous leukemia. [16] The body may have a selective sensitivity to this drug with skin being more sensitive than other systems. A normalization of keratin expression in psoriatic plaques has been found in patients who take hydroxyurea. [14]

Contraindications of hydroxyurea:

Absolute contraindications are pregnancy and lactation (Category D) and hypersensitivity to hydroxyurea. Relative contraindication are concomitant administration of cytarabine (ara-C), blood dyscrasias (particularly those involving diminished counts), unreliability or emotional/ mental impairment, substance abuse, ongoing infection, hepatic/renal/cardiopulmonary disease, psoriatic arthropathy and unstable/fulminant psoriasis. [14]

Therapeutic use in Dermatology:

US food and drug administration approved indications are squamous cell carcinoma of the head and neck (rare use) and metastatic melanoma and gastro-intestinal melanoma (rare use). "Off-label" usages are severe psoriasis, pyoderma gangrenosum, sweet syndrome, cryoglobulenemia, scleromyxedema and hyper-eosenophilic syndrome, described by Whitney and James. [14]

Indication of hydroxyurea in psoriasis:

Patients unresponsive to more conventional therapy of psoriasis (topical corticosteroids, tars, anthralin, UVB) and patients who may not be acceptable candidates for more extensive/toxic treatments (PUVA, methotrexate, etretinate, cyc1osporine), suggested by Boyd and Nedlner. [14]

Adverse reactions of hydroxyurea:

Hydroxyurea is usually well tolerated. One study showed that 57% of patients who received 1.5 gm/day of the drug experienced no adverse effects and that only 18% had side effects significant enough to necessitate stopping the medication. Authors noted no deaths or serious toxicity in more than 100 psoriasis patients treated with hydroxyurea. Older patients are more prone to have side effects. Oral administration of the drug results in more toxic events than intravenous administration. [14]

Hematologic effect

The most common adverse effect with hydroxyurea is myelosuppression. Mild megaloblastic changes are

ubiquitous among patients receiving hydroxyurea and are not a reason for discontinuance. Frank anemia present in 12-34% of treated patients, leucopenia in 7% and thrombocytopenia in 2-3%. Myelosuppression due to hydroxyurea resolves rapidly on discontinuation, from the study done by Whitney and James. [7]

Gastrointestinal effects

Hepatitis with elevated bilirubin and transaminases has been described by some investigators but not others. Irreversible hepatic damage has not occurred and liver biopsy specimens have not shown fibrosis. Patients may also complain of mild to moderate nausea, vomiting, and anorexia. [7]

Renal effects

Hematuria and an elevated blood urea nitrogen value have been reported. Layton et al. studied renal abnormalities in patients given 40 mg/kg/day and found instances of albuminuria, pyuria, cast formation, and mild suppression of tubular function. Recently, kidney failure developed in two patients who received hydroxyurea, 0.5 to 1.5 gm/day, for polycythemia vera. At high doses (100 mg/kg/day) a uricosuric effect is noted.[12] One long-term study of hydroxyurea administration in psoriasis demonstrated no renal dysfunction by Jeffrey.[14]

Teratogenicity

The initial report about the teratogenicity of hydroxyurea described its use in animals. Pregnant female rats given the drug produced malformed embryos. Other animal models have shown numerous chromosomal abnormalities. A subsequent article documented central axis deformities and spina bifida. Currently, hydroxyurea is considered to be a powerful teratogen.[14] Hydroxyurea is a category D agent during pregnancy, and use is generally avoided. There is a single report of hydroxyurea use for polycythemia vera during pregnancy without any apparent fetal or neonatal complications, suggested by Whitney and James. [7]

Cutaneous side effects

Hydroxyurea does not appear to produce many cutaneous side effects. A "skin rash" was initially reported that was severe enough to necessitate stopping the medication. Hydroxyurea has also been suspected of causing a fixed drug eruption, stated by Jeffrey.[14]

Of the important cutaneous side effects are dermatomyositis-like eruption, a lichenoid drug eruption, leg ulcers, photosensitivity with radiation recall, and hyperpigmentation of the skin and nails, suggested by Whitney and James.[7] Alopecia, if it occurs at all, is transient and only minimally severe. Additional mucocutaneous findings include onycholysis, onychodystrophy, palmar and plantar keratoderma, oral ulcerations, stomatitis, palpable purpura, xerosis, and cutaneous vasculitis. [14]

Neoplastic effects

The medication has been rarely associated with the development of acute leukemia. Non-melanoma skin cancers, including basal cell carcinoma and squamous cell carcinoma have also been reported by Perlis et al. [13]

Safety and monitoring for use of hydroxyurea:

Initial evaluation: Careful history and physical examination, identification of proper patient characteristics and risk factors and survey for interacting medication (Cytarabine).

Baseline laboratories: CBC with differential and platelets, basic serum chemistry profile, urinalysis, renal function testing (Creatinine or blood urea nitrogen)

Ongoing laboratory monitoring: Complete Blood Cell (CBC) with differential and platelets, perform weekly initially, then transition to biweekly or monthly after one month, perform testing with dose escalation, decrease/discontinue if hemoglobin decreases by 3g/dl, white blood count < 4000/mm^3, or platelets < 100,000/mm^3, Serum chemistry and urinalysis, perform monthly initially, then transition to every 3-6 months if stable, perform testing with dose escalation described by Whitney and James. [7]

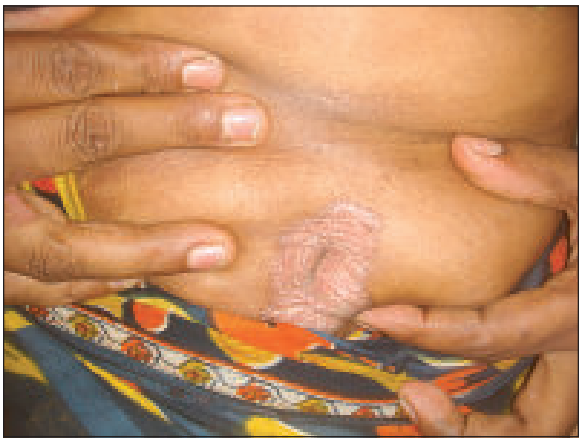


Fig.-3: *A female patient of psoriasis with a well circumscribed erythematous plaque and silvery scale around the umbilicus.*

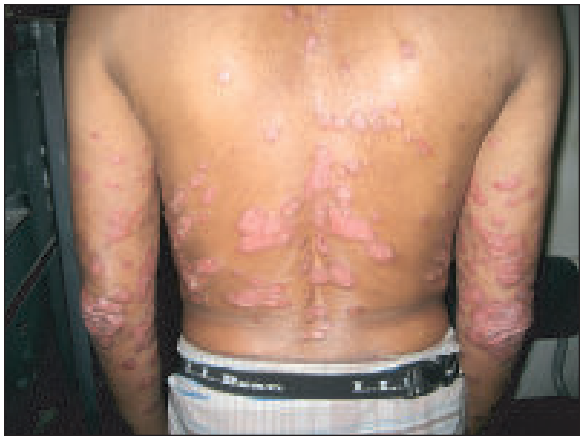


Fig.-4: *A male patients of psoriasis with multiple erythematous plaques and papules, along with silvery scale in trunk and upper extremities.*

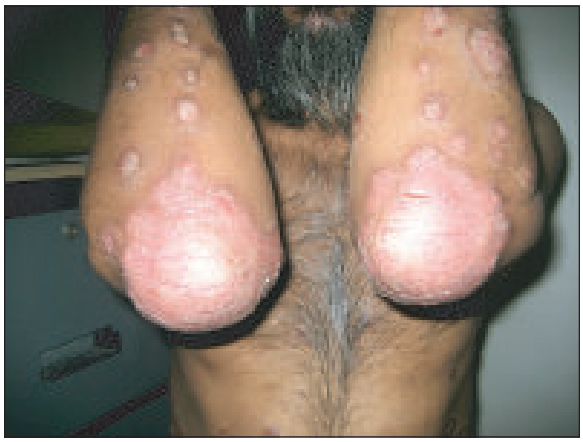


Fig.-5: *A male patients of psoriasis with multiple erythematous plaques and papules, along with silvery scale in upper extremities.*

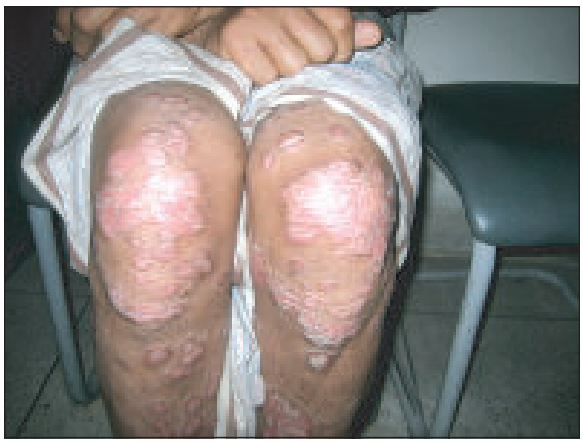


Fig.-6: *A male patients of psoriasis with multiple erythematous plaques and papules, along with silvery scale in lower extremities.*

Role of hydroxyurea in psoriasis:

In 1970 Leavell and Yarbro published the first double-blind study on the use of hydroxyurea to treat psoriasis. The authors noted improvement both clinically and histologically in 9 of 10 patients. Several smaller studies soon followed and showed favorable results.[10] The first report of a larger number of patients came in 1973 when Kevin published their paper on 60 psoriasis patients given hydroxyurea intermittently for 18 months. These patients were treated with 1to 1.5 gm daily. The investigators noted good to excellent results in 63%. Seventeen percent noted a poor response. [17] A follow-up report 3 years later by Jeffrey described similar results in a total of 92 patients.[14]

Kipnis et al. treated 85 therapy-resistant psoriasis patients starting at 1.5 gm/day. A 61% rate of "satisfactory remission" was noted.[12] Jeffrey combined the use of hydroxyurea and methotrexate in 14 patients with severe psoriasis and noted an "adequate response" in 13 patients. Topical hydroxyurea has also been investigated. Plaque psoriasis responded to the application of a 10% cream but *only* with continuous occlusion. The authors concluded that a topical formulation of this drug was of little value.[14]

Certain types of psoriasis may respond better than others. Most studies have concentrated on the plaque form of the disease. Stein et a1. treated four patients with pustular psoriasis with 1 to 2 gm/day and noted good clearing in all. [11] Leavell and Yarbro also described two patients with generalized pustular psoriasis who responded impressively to administration of hydroxyurea.[10] Other investigators, have not found the drug to benefit pustular disease. Authors treated 13 patients with pustulosis palmaris et plantaris without improvement. Psoriatic erythroderma and guttate psoriasis have responded to hydroxyurea.[14]

Kumar et al. treated 31 patients with 1-1.5g/day with a median duration of 36 weeks. A 74.2% patient showed at least adequate response (35-70% fall in PASI), 55% patient showed good response (70-90% fall in PASI) and complete or almost complete clearance (>90% fall in PASI) was achieved in 26%. Twenty-five patients followed up for a mean duration of 36.1+/- 13.8 week (range 4-120 weeks) after stopping treatment. Of the 18 responder on regular follow up 50% relapsed at mean follow up duration of

16+/- 8.4 weeks. The others continue to be in remission and are on regular follow up. [18]

Sharma et al. treated 34 patients with 1-1.5g/day over 16 months. Good to excellent response (excellent, >75-95% clearance; good, >50-75% clearance) was observed in 73.5%, less than 50% response in 20.6% patients. Therapy was discontinued in 3 patients due to leucopenia that recovered on discontinuation of hydroxyurea. Patients were followed up to 1 year and relapse was observed in 5 patients. The duration of remission varies from 6 months to 1 year.[19]

Ranjan et al. done a comparative study of 2 groups of 15 patients with weekly doses of methotrexate (15-20mg/week) or hydroxyurea (3-4.5g/week) for 12 weeks. A 66.66% patient in the methotrexate group achieved > 75% reduction in the PASI score, while in the hydroxyurea group only 13.33% patients showed similar results, signifying that methotrexate leads to a faster clearance of the disease. The methotrexate related side effects, however, were also higher. [20]

An evaluation of the efficacy of hydroxyurea is difficult because various investigators have used different doses for varying time intervals and evaluated their patients by different criteria. Overall, a favorable outcome has been reported in 45% to 63% of treated patients and excellent results in 18% to 38%. Fifteen to twenty percent have had a poor result. Not all investigators have found hydroxyurea to be of benefit. Feldman reported that only 13 of 86 patients (15%) originally started with the drug were able to use it for long-term maintenance therapy. Thirty-four patients (40%) subsequently relapsed, 29 (34%) were treatment failures, and 10 (11%) discontinued the drug because of side effects. [21]

Hydroxyurea does not appear to improve significantly the natural course of psoriasis. However, McDonald found that 20% to 30% of his hydroxyurea-treated psoriasis patients experienced a longterm remission of their disease. Other authors have found that none did.[13] Kormeli and Leavell and Yarbro in their early studies found no patients experienced are bound flare when the drug was stopped but both study populations were small. [9,10] Kevin in his analysis of 92 patients found an incidence of 5%. It had been thought that patients who failed to respond to methotrexate or PUVA would be unlikely to benefit from hydroxyurea but this notion has since been refuted for both systemically and topically recalcitrant disease. An occasional adverse effect on psoriasis has been reported.[17] Most studies have shown the maximum effect of hydroxyurea to occur 4 to 8 weeks after treatment was begun, although in pustular psoriasis an earlier response is possible. [14]

Conclusion:

The efficacy and safety of hydroxyurea is equal to better than methotrexate, it can be used as a monotherapy or as an effective pair or in combination therapy or rotational therapy. Bangladesh is a developing country and majority of the people are in low socioeconomic condition. Hydroxyurea is relatively inexpensive, contraindications are few and it is relatively less toxic and easily available in Bangladesh. The potential toxic effects of long term use of the classic anti-psoriatics, long continuous therapy, higher cost and low socio-economic conditions of patients justify the use of hydroxyurea in Bangladesh.

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