Infliximab in the treatment of severe psoriasis vulgaris

Abstract:

Psoriasis is a chronic, immune mediated inflammatory disease. The inflammatory activity of the psoriasis plaques is partially triggered by activation of the Th1 lymphocytes, which release pro-inflammatory chemokines and cytokines such as tumor necrosis factor alpha (TNF-α). Infliximab is a mouse-human chimeric monoclonal anti body that neutralize the biologic activity of TNF-α by binding to soluble and transmembrance forms of this cytokine and inhibiting it's binding to the receptors. We aim to assess the efficacy and tolerability of infliximab in severe psoriasis vulgaris.

Materials and Methods: Twenty patients were included in the study, 12 men and 8 women with severe psoriasis vulgaris, were assigned infliximab infusion 5 mg/kg at weeks 0, 2 and 6, followed by maintenance therapy every 8 weeks. For every patient psoriasis activities and treatment efficacy were assessed by measuring Psoriasis Area Severity Index (PASI) scores
Results: Among the 20 patients enrolled in this study, 2 patients are dropped out from the study after first dose due to hypotension or mild urticarial reactions. Eighteen patients had completed the course of treatment for 32 weeks. Maximum PASI score at baseline was 64 and minimum PASI score was 14 (Mean PASI score was 32.88 ±10.871). PASI score was greatly reduced from 32.8 to 16.2 in 6 weeks and to 2.2 in 10 weeks time. 50% improvement at the after the 1st dose (2 weeks) in 8 patients (45.5). In 10 patients (54.5%), 75% improvement in PASI score from baseline at tenth week. About 90% improvement in PASI score in most of our patients (16) at sixteenth week and all patients had complete clearance at twenty 24th week and 32 weeks of treatment. The acute adverse effect was infusion reactions were reported in one patient during the initial 1ST week, and hypotension which occurred at week 2 this lead to discontinuation of the drug. Infections manifested as delayed adverse effects where 2 of 18 patients (11.1%) developed UTI at week 2nd and week 16th also another patient at week 6 developed URTI & UTI from week 0. All reported infections were mild and treated during the course.
In conclusion, infliximab was found to be safe and effective and well tolerated in the treatment of recalcitrant plaque psoriasis. To the best of our knowledge this is the first study to be published in Libya and North Africa.

Keywords: Psoriasis vulgaris , Infliximab, Safety, Tolerability

Introduction

Psoriasis is a distressing, chronic immune mediated, inflammatory disease that affects skin and joints. It is characterized by infiltration of the skin by activated T cells, abnormal keratinocyte proliferation, cytokines, chemokines, and excessive production of tumor necrosis factor (TNF) in the psoriatic lesion(1). Estimates of the prevalence of psoriasis vary from 2% to 3%, with rates varying between countries and races (2). Burd 2006 (3) has been found that, a quarter of patients develop the disease

before the age of 20 years. A further peak in incidence is recorded in the fifth and sixth decades. A study done by Lebwohl 2003,where he has been observed that, men and women are equally frequently affected. Caucasians are more commonly affected than other ethnic groups (4).

Clinically have been found that, around 80% of individuals present with chronic plaque psoriasis characterized by well demarcated, red, thickened patches of skin which become elevated and covered with an adherent, silvery scale (5). Typically plaques are located on the extensor aspect of knees, elbows, hairline, scalp, intergluteal cleft and lumbosacral area.(6).

Infliximab belongs to the class of biological response modifiers called tumor necrosis factor (TNF-α) blockers, with human constant regions and murine variable regions. It engineered from human and mouse antibody molecules. It works by directly binding to both transmembrane and soluble TNF-α molecules in the blood and diseased tissue. with high affinity, specificity, and avidity.(7) TNF-α levels are elevated in psoriatic plaques, which supports the rationale of using infliximab and other TNF-α antagonists in psoriasis. Infliximab binds soluble TNF-α and TNF-α that has already bound to its receptor (8). Through TNF-α blockade, infliximab inhibits many key cells in the inflammatory response, leading to a decrease in the proinflammatory cytokines that propagate chronic inflammation. In psoriasis plaques, levels of TNF-α, as well as the numbers of T cells, are reduced following infliximab infusion (9)

Our aim in this study was to assess the efficacy and tolerability of infliximab monotherapy in Libyan patients with severe psoriasis vulgaris and to report any adverse effects."

Materials and methods:

Twenty adult patients who had sever psoriasis vulgaris involving more than 10% of the body surface area, and who had received systemic therapy for psoriasis previously were enrolled in cohort study over one year at dermatology department Jamhoria hospital, Benghazi-Libya. All patients signed an informed consent form before participating in the study. Each patient underwent a detailed medical history, clinical and laboratory assessments were carried out as screening baseline, including complete blood count, biochemistry, urine analysis, serum for human chorionic gonadotrophin concentration, chest x- ray, tuberculin test to exclude tuberculosis, serological examination including HIV, HBV and HCV,ANA according to proforma. Clinical assessment and PASI score were carried out for all patients. Infliximab is commercialized in a sterile vial in the form of a white powder that has to be diluted in 10 ml of distilled water; each vial contains 100 mg of infliximab for intravenous administration which is carried out in a hospital by a doctor or a specialist nurse. It is given in a dose of 5 mg/kg mixed with 250 ml saline solution as a slowly intravenous infusion (over a 2- hour period) followed by two more doses at weeks 2 and 6 (induction phase) and then every 8 weeks (maintenance phase)

To minimize the risk of side effects, the patient is given 2 tablets of paracetamol, antihistamine and hydrocortisone injection just before the infusion. Careful observation of the patient should be done during the infusion and for two hours afterwards to ensure that the patient will not develop any allergic reactions. The treatment effect is assessed at each visit clinically where PASI score is calculated and laboratory investigations including complete blood count, liver function test, renal function test, urine analysis taken two weeks before the dose. If no response after 14 weeks (i.e. after 4 doses), infliximab is

stopped. Statistical analysis was carried out using Statistical Package for the Social Sciences (IBM SPSS) version 1."

Results:

Among 20 patients included in this study 12 (60%) were males and 8 (40%) were females.. The patients age was ranging from 27 to 51 years (Mean:37.85 years ± 6.815year). All patients received infliximab 5 mg/kg IV infusion and two patients were withdrew during the course of the study. One patient was withdrawn at week 2 due mild urticarial reaction and the other patient because of hypotension after her first dose. Regarding to disease duration ranging from 2 to 37 year (Mean:14.90 year ±8.25year). Most of disease duration (30%) was between 10-14 year (Fig.1). A bout 12 patients were previously treated with systemic treatment such as methtrexate or cyclosporine. Maximum PASI score at baseline was 64% and minimum PASI score was 14%, (Mean PASI score: 32.8). Therapeutic response showed a dramatic reduction in PASI score where it became 16.2 after 6 weeks (third dose) and more reduced to 2.2 at 10 to 16 weeks (Fig: 2). At the second dose, 50% improvement was seen 7 patients (38.8) and only 2 patients (11.1%) had 75% improvement. By 6 weeks (third dose), 75% improvement was achieved in 11 patients (60%), in 16 patients (88.8%) at 10^{th} week and almost all patients by week 16 (Fig.3) At week 24,and 32 , all patients were completely cleared and 90% - 100% improvement was reported in all treated cases as seen in Fig.4 (a), (b), (c) and Fig.5 (a) and (b). There was no any serious adverse effect. Mild UTI was observed in 2 patients (11.1%).. Acute urticarial reaction was reported in one case and hypotension in another and both cases were dropped from the study. Upper respiratory tract infection was seen in 2 cases. All infections were mild and treated during the course.

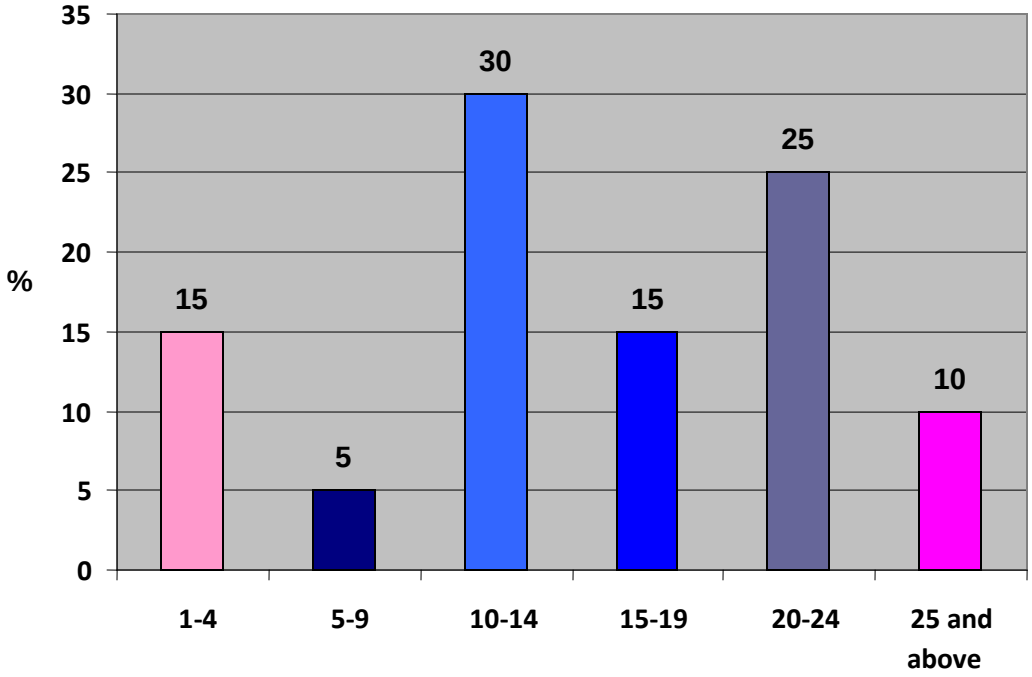

Figure 1: Psoriasis in years

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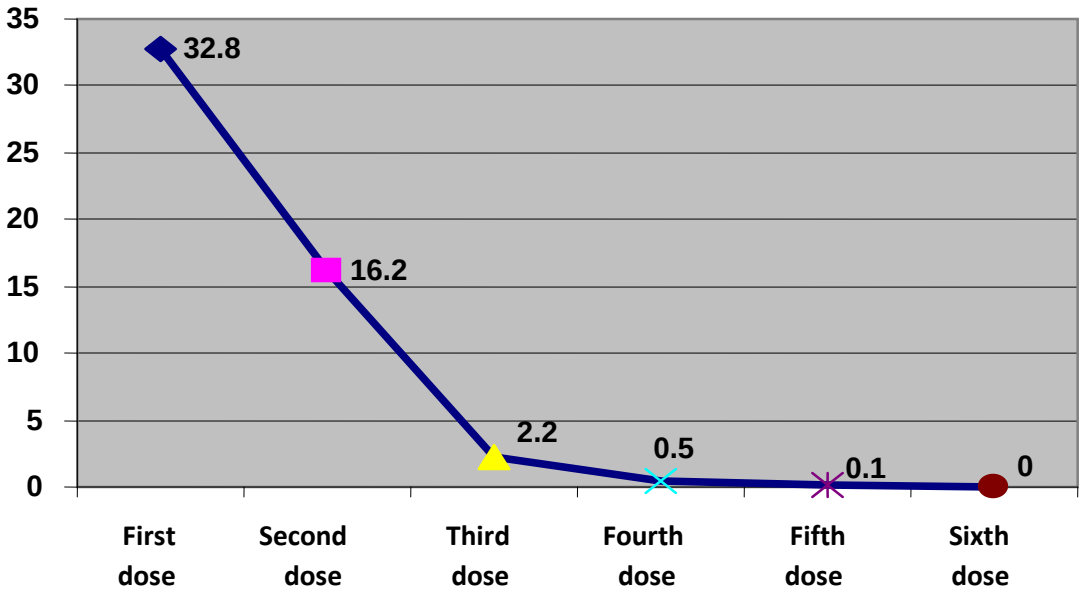

Figure 2: Changes in the mean PASI score during the treatment coarse

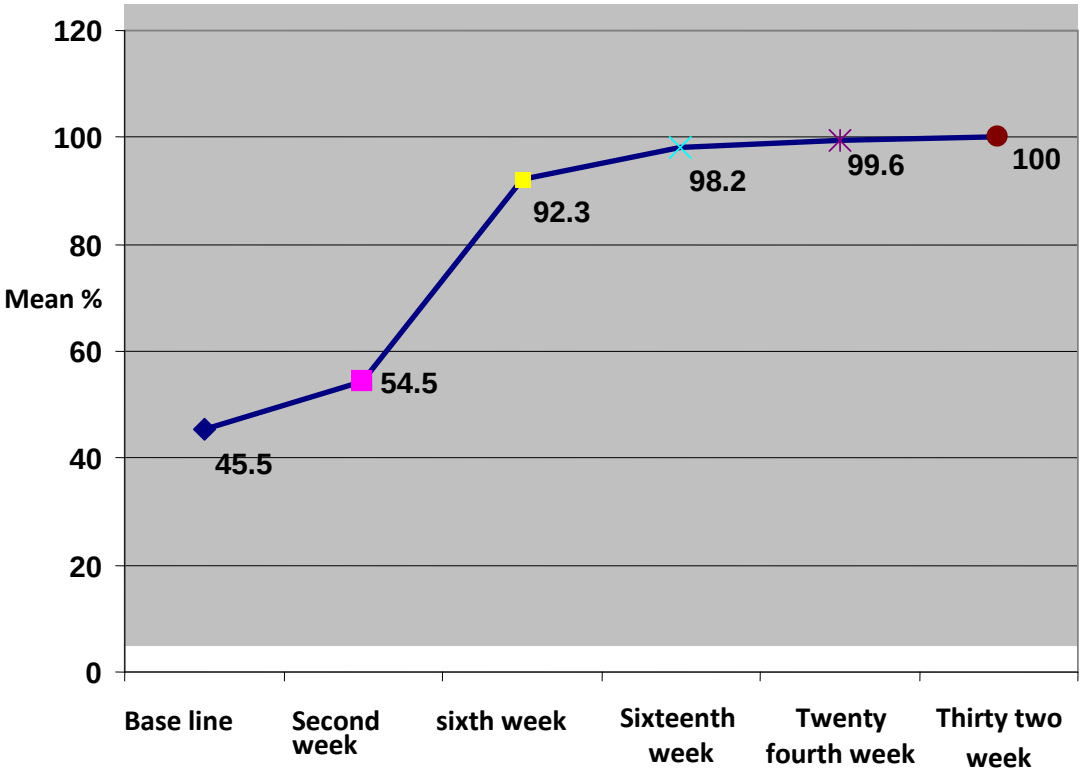

Figure 3: Mean percentage of PASI improvement

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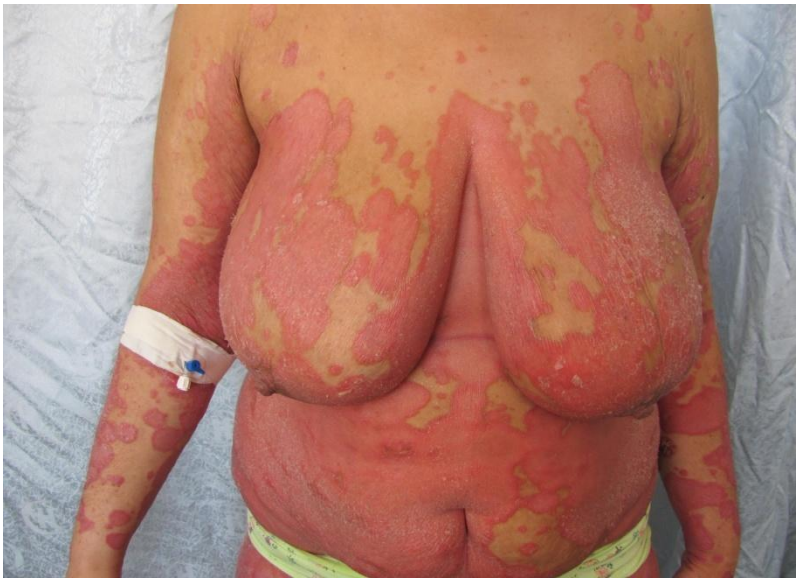

Figure 4 (a) : Extensive and severe psoriasis (baseline PASI).

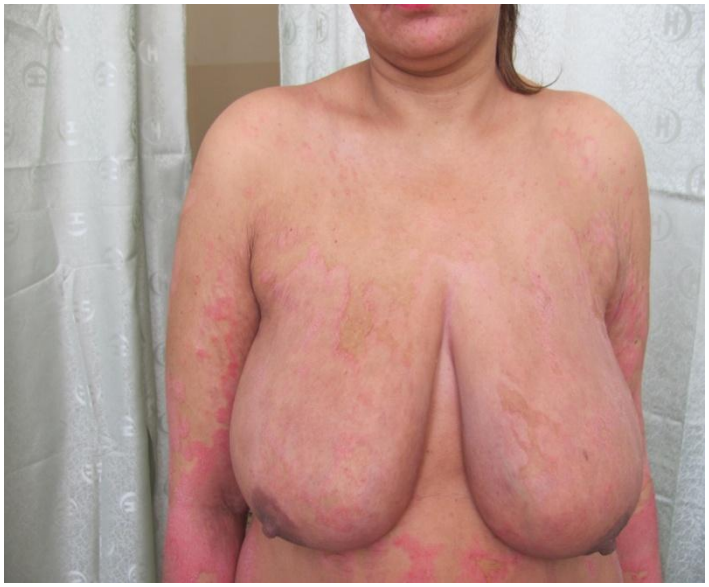

Figure 4 (b) : Dramatic improvement (6th week).

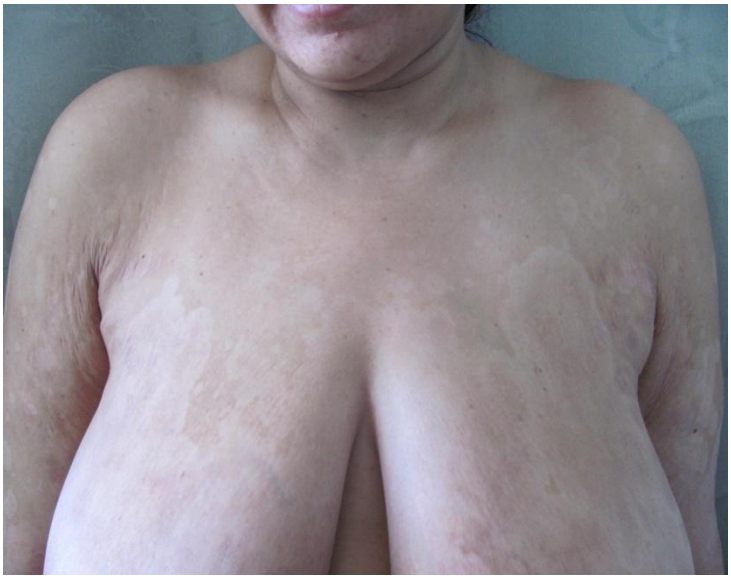

Figure 4 (c) : Total clearance, >90%PASI improvement (32 week).

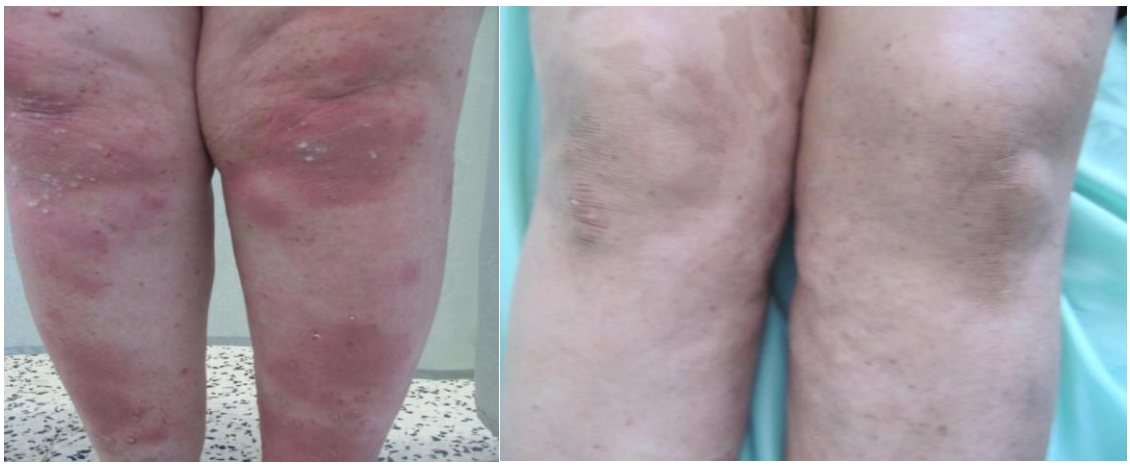

Figure 5: (a) Extensive and extensive psoriasis (baseline PASI), (b): Total clearance (32 week)

Discussion:

Psoriasis is a distressing, chronic immune mediated, inflammatory disease that affects skin and joints. It is characterized by infiltration of the skin by activated T cells, abnormal keratinocyte proliferation, cytokines, chemokines, and excessive production of tumor necrosis factor (TNFα) in the psoriatic lesion(1).

During the last decade, a better understanding of psoriasis has been achieved and it is now known that psoriasis is a T-cell mediated disease. Tumor necrosis factor-α (TNF-α) plays a central role in the pathogenesis of psoriasis and its expression is notably increased in both serum and skin lesions of psoriatic patients (6). So the treatment of psoriasis has undergone a revolution with the advent of biologic therapies, including infliximab, etanercept, adalimumab, efalizumab, alefacept and more recently , secukinumab, guselkumab and brudalomab (10,11,12).

Regarding psoriasis Area Severity Index (PASI) is considered by many to be the gold standard severity assessment tool and consists an average measure of 4 parameters; redness, thickness and scaling of lesions and extent of disease (13,14). The mean PASI score at baseline was 32.8 which show a marked decrease at third dose (6^{th} week) where it became 2.2 and reached zero at sixth dose (32^{nd} week), the mean percentage of PASI improvement at base line was 45.5% and had shown marked improvement at third dose (6^{th} week) and reached total clearance at sixth dose (32^{nd} week), as compared our study with finding by Chaudhari 2001 (15) the mean PASI at base line was 17.5 with marked decrease at (2^{nd} week) ; recently, he had reported on the pivotal role of infliximab in alleviating psoriasis. Nine of 11 patients (82%) and 10 of 11 patients (91%) who were randomly assigned to receive infliximab at dosages of 5 mg/kg and 10 mg/kg respectively (given at weeks 0, 2 and 6) showed significant improvement of the psoriatic skin lesions in comparison to only 2 patients (18%) who received placebo. Interestingly, extension of this study for 6 months on an open-label basis demonstrated that 16 of the 29 patients who received infliximab maintained a 50% improvement of their Psoriasis Severity Index score . Similar results were also obtained using 5 mg/kg of infliximab (with maintenance doses of 3 mg/kg). After 10 weeks of therapy 8 patients improved by 70% (ACR70), and magnetic resonance imaging revealed an 82.5% mean reduction in inflammation from baseline with a remarkable reduction in the psoriasis area and PASI score (15). Infliximab is effective in both the induction and maintenance phases of treatment. Various clinical trials have demonstrated the efficacy of infliximab in moderate-to-severe psoriasis. Infliximab not only clears the skin lesion but also significantly improves the health-related quality of life.(16). 50% improvement in PASI had been observed in 6 (33.3%) patients out of 18 after first dose and 7 patients (38.8%) showed improvement in PASI after 2^{nd} dose .75% improvement in PASI was observed in one patient (5.5%) after first dose, 2 patients (11.1%) at second dose, 7 patients (38.8%) at third dose and 2 (11.1%) patients at fourth dose, as compared our study with finding by Reich et al 2005 study of 378 patients with severe psoriasis vulgaris 75% improvement in PASI occur after 10^{th} week in 80% of patients(17). A total of 30 patients were followed during the open-label extension, 29 of whom received Infliximab 5 mg/kg or 10 mg/kg. Among all patients treated with infliximab, 57% and 50% of patients were able to maintain ≥ 50% and ≥ 75% improvement in PASI scores,

respectively, at week 26. Nine patients who initially responded to infliximab were retreated after experiencing a relapse of symptoms. PASI scores improved with retreatment, but not to the same extent as was observed with the initial induction regimen. A dose-response relationship was suggested with regard to the duration of clinical benefit. In general, patients receiving infliximab 5 mg/kg began losing response after week 14, whereas patients receiving infliximab 10 mg/kg began losing response after week 18 (18). 90% improvement in PASI was observed at 2nd week by 2 patients (11.1%), 11 patients (61.1%) at 6th week, 16 patients (88.8%) at week 16th and at 24th week all patients had 90% improvement, as compared this finding with Reich et al 90% improvement occur in 57% of patients (19). Infliximab had been generally well tolerated and available for clinical use in adult. Although infliximab is generally well tolerated, there are some adverse effects associated with its use. Adverse events are a major reason for discontinuation of infliximab therapy in patients with psoriasis. A Canadian multicenter retrospective study showed that 15% of patients withdrew from infliximab therapy owing to adverse effects. (20) Infusion reactions occur in about 3–22% of patients of psoriasis treated with infliximab. (21) The acute adverse effect was infusion reactions reported in 1 (5%) of patients during the initial first week of treatment and hypotension in one patient (5%), this lead to discontinuation of the drug ,as compared our study with Kipnis et al infusion reactions were reported in 20% of patients receiving infliximab (22). UTI was the adverse event that occurred in a higher proportion (11.1%) at 2nd week and week 16th also another patient at week 6th developed URTI & UTI . All delayed adverse effects were followed up and treated without the drug having to be interrupted. Urticaria was the most common of the acute infusional reactions. Some authors do not consider this reaction to be anaphylactic and the few studies conducted on this subject revealed only one case in which there was an increase in IgE antibodies (23,24). Durate AA, Chebin FB were observed, the four patients who developed urticaria at the first infusion obtained complete remission of the symptoms after the velocity of the infusions was reduced and an ampoule of promethazine hydrochloride was administered intramuscularly. Symptoms such as tachycardia, sweating, increased arterial pressure and cooling of the limb into which the infusion was given, which were observed during our clinical experience, have also been reported as acute adverse events in the literature; however, the mechanism through which this occurs is unknown. Some investigators consider them anaphylactoid reactions, i.e. not immune reactions (25). The increases in blood pressure were treated with 25 mg of captopril, while the other symptoms were resolved by reducing the velocity of the infusion (26).

In conclusion, infliximab was found to be effective and safe for treatment of severe psoriasis vulgaris .and has a rapid induction phase in which 75% of PASI improvement was reported at 3rd dose (6 week) in about 88.8 %. To the best of our knowledge, this is the first publication about use of infliximab in psoriasis in Libya and North Africa.

Author contributions : All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Conflicts of Interest ; The authors report no conflicts of interest in this work

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