REVIEW

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Dermatologic adverse events: Golimumab, friend or foe?

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Golimumab is a fully human anti-TNF-α blocker that has demonstrated its efficacy in the treatment of numerous kinds of diseases. Although it is generally safe and well tolerated, various adverse events have been reported. The present aim is to improve the understanding of dermatologic adverse events associated with golimumab following a search of various scientific databases. This systematic review and meta-analysis shows that golimumab is associated neither with severe injection-site reactions nor with injection-site erythema. We found no significant lupus-like syndromes, and no significant skin squamous cell carcinoma. We further suggest systematic dermatologic monitoring in clinical practice during golimumab therapy. Subsequent research should employ a larger cohort of patients to ensure clear and significant future conclusions.

1. Introduction

TNF-α blockers are efficient biologic drugs designed for inhibition of the cytokine TNF-α in its soluble and/or transmembrane form in different kinds of diseases (Shealy et al. 2007). Despite the safety and good tolerability of these biologic agents, a number of adverse events have been reported. The major adverse effects associated with these blockers are infections such as tuberculosis, invasive fungal infections, and also opportunistic infections (Hussar 2009). Serious and sometimes fatal infections have also been found in different clinical trials using these biologic agents (Food and Drug Administration 2009b), and other co-morbidities relating primarily to malignancy and immunogenicity have been associated with them. However, actual literature data are insufficient and too biased to confirm a close and definite association between these drugs and the reported co-morbidities (Zidi et al. 2010). Hence, it is reasonable to suppose that golimumab, a fully human anti-TNF-α antibody recently approved by the US Food and Drug Administration (FDA), has the same adverse events. In fact, it seems that golimumab has the same overall pattern of adverse events and co-morbidities. In this systematic and meta-analytic study, we investigated dermatologic adverse events manifested in golimumab trials. Here, we summarise current knowledge of the possible association of golimumab with monitored dermatologic adverse events. Moreover, we discuss the role of golimumab as a friend or a foe in the therapy of rheumatoid arthritis (RA), psoriatic arthritis (PA), and ankylosing spondylitis (AS).

2. Methods

Clinical trials dealing with golimumab and dermatologic adverse events were systematically checked in various databases like Cochrane library, EBSCO, Highwire, and PubMed. We also searched both the FDA database (http://www.fda.gov) and MedWatch (the FDA safety information and adverse event reporting program, http://www.fda.gov/Safety/MedWatch/default.htm) for further alerts on golimumab. The search terms used were as follows: Golimumab, Simponi, CNTO 148, CNTO148, CNTO-148. We focused only on studies in the French and English languages. Publications were retrieved up to March 2010.

3. Results and discussion

Anti-TNF-α agents are undoubtedly prescribed for the treatment of diseases like rheumatic diseases, Crohn's disease and dermatologic diseases like psoriasis (Moustou et al. 2009). The efficacy of these agents in dermatologic diseases has been proved, for example infliximab (Chaudhari et al. 2001; Krüger-Karasagakis et al. 2006; Markham et al. 2006), etanercept (Altomare et al. 2008), adalimumab (Bongiorno et al. 2008), and golimumab (Rozenblit and Lebwohl 2009). However, some anti-TNF-α blockers may aggravate dermatologic diseases and may be associated with various dermatologic reactions (Lee Kavanaugh 2005; Thielen et al. 2005; Graves et al. 2007; Davaine et al. 2008). In fact, several case reports have demonstrated erythema multiforme after adalimumab (Ahdout et al. 2010; Food and Drug Administration 2009a), and also after etanercept treatment (Ahdout et al. 2010). Moreover, other cutaneous manifestations like dermatitis have been reported (Deng et al. 2006). It has recently been shown in a study by Moustou and collaborators that anti-TNF-α agents have been strongly associated with infusion/injection-site reactions, psoriasis, psoriasis-like lesions, lupus-like syndromes, vasculitis and cutaneous infections (Moustou et al. 2009). A moderate association only was found with eczematous and lichenoid reactions, and granulomatous diseases (Moustou et al. 2009).

No systematic cutaneous examinations were performed in clinical studies of golimumab therapy. The whole of the data are

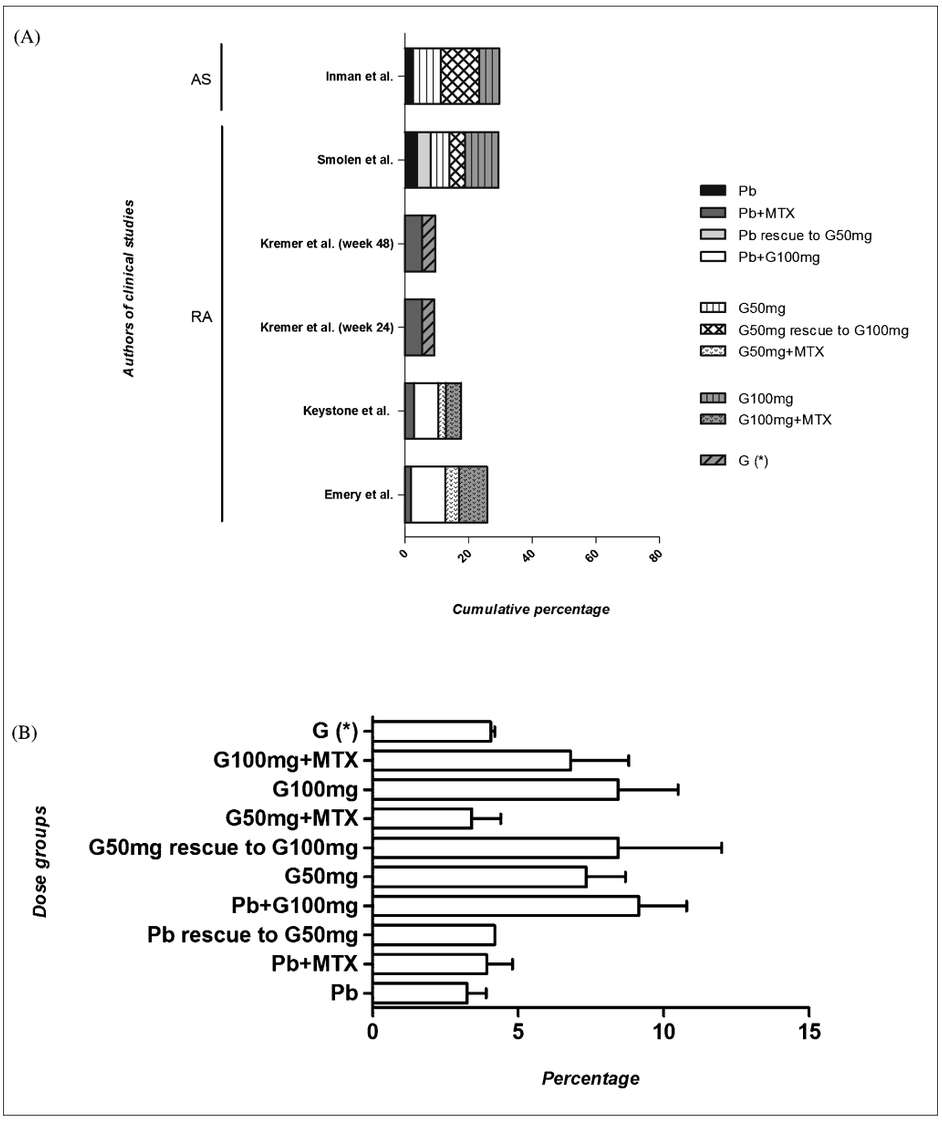

Fig. 1: Injection-site reactions percentage distribution in different clinical studies after golimumab therapy in patients with rheumatoid arthritis and ankylosing spondylitis. (A) Monitored cumulative percentage with their corresponding authors. (B) Mean of monitored percentage ± SEM Abbreviations: AS = Ankylosing spondylitis, ev = every, G = Golimumab, MTX = Methotrexate, Pb = Placebo, RA = Rheumatoid arthritis, (*) All dose groups in the study of Kremer et al.

summarized in the Table. Only five studies reporting injection-site reactions (not counting injection-site erythema) have been done (Fig. 1). There were four studies performed with RA patients and one with AS patients. One relevant point regarding the studies cited is the fairly small patient cohorts, except for the study by Kremer et al. (2010), which included a relatively large number of patients (626).

Examination of the cumulative percentage of injection-site reaction in each study showed, interestingly, almost the same cumulative percentage across all dose groups in the studies by Inman et al. (patients with AS) and Smolen et al. (2009, patients with RA previously treated with other TNF-α blockers). The cumulative percentages were 29.7% (mean ± SEM, 7.4 ± 2, n = 4) and 29.5% (5.9 ± 1.2, n = 5) for the Inman et al. (2008) and Smolen et al. (2009) studies, respectively. However, the internal variation between the dose groups was not always similar (Fig. 1B).

When we consider the common doses of golimumab (in patients naïve to any TNF-α blockers), we notice that the cumulative percentage of injection-site reactions was different. This percentage was found to be 9.3% (4.7 ± 0.8, n = 2) at week 24 and 9.6% (4.8 ± 0.6, n = 2) at week 48 in the study by Kremer et al. (2010), 17.7% (4.4 ± 1.1, n = 4) in the study by Keystone et al. (2009), and finally 25.9% (6.5 ± 2, n = 4) in the study by Emery et al. (Fig. 1A). We conclude, as do Davaine and collaborators, that these discrepancies depended on the authors (Davaine et al. 2008).

In Fig. 1B, the mean percentage of injection-site reactions, in all diseases confounded, was not high, with a maximum of 9.15% in the group of patients treated with placebo and golimumab (100 mg). The lowest mean percentage of injection-site reactions was found in the placebo group (3. 3%), followed by the group of patients treated with golimumab (50 mg) combined with MTX (3.4%). This result is in accordance with the conclusion of Storage et al. that patients receiving either golimumab alone or golimumab combined with disease-modifying anti-rheumatic drugs (DMARDs) manifested more adverse skin events (Storage et al. 2010).

The other groups showed various percentages of injection-site reactions: 3.9% in the group of patients treated with placebo

Table: Incidence of dermatologic adverse events in clinical trials of golimumab therapy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis

Study name *(Author and date of publication)*	Treated disease	Treatments *(Number of patients)*	Kind of dermatologic adverse events *(Group)*	Number of dermatologic adverse events *(%)*
Kay et al. (2008)	RA	MTX + placebo *(35)*	Injection-site erythema *(MTX + Placebo, Golimumab (50 mg) every 4 weeks + MTX, Golimumab (50 mg) every 2/4 weeks + MTX, Golimumab (100 mg) every 4 weeks + MTX, Golimumab (100 mg) every 2/4 weeks + MTX)*:	24: 4 of 34 *(11.8),* 5 of 37 *(13.5),* 2 of 32 *(6.3),* 3 of 33 *(9.1),* 10 of 35*(28.6):*
		Golimumab (50 mg) every 4 weeks + MTX *(35)*	-pruritus *(group treated with Golimumab)*	-NR *(3.6)*
		Golimumab (50 mg) every 2 weeks + MTX *(34)*	-pain *(group treated with Golimumab)*	-NR *(2.9)*
		Golimumab (100 mg) every 4 weeks + MTX *(34)*	-induration *(group treated with Golimumab)*	-NR *(2.2*
		Golimumab (100 mg) every 2 weeks + MTX *(34)*	-burning *(group treated with placebo, with Golimumab)*	-NR *(2.9, 1.5)*
			-hemorrhaging *(group treated with placebo, with Golimumab)*	-NR *(5.9, 1.5)*
			-stinging *(group treated with Golimumab)*	-NR *(1.5)*
			-urticaria *(group treated with Golimumab)*	-NR *(1.5)*
			-swelling *(group treated with placebo,with Golimumab)*	-NR *(0.7)*
			Lupus-like syndromes	0
Emery et al. (2009)	RA	MTX + placebo *(160)*	Injection-site reaction *(MTX + placebo, Golimumab (100 mg) + placebo, Golimumab (50 mg) + MTX, and Golimumab (100 mg) + MTX)*	41: 3 of 160 *(1.9),* 17 of 157 *(10.8)*, 7 of 158 *(4.4),* and 14 of 159 *(8.8)*
		Golimumab (100 mg) + placebo *(159)*	Injection-site erythema *(Golimumab (100 mg) + placebo, Golimumab (50 mg) + MTX, and Golimumab (100 mg) + MTX)*	28: 11 of 157 *(7)*, 8 of 158 *(5.1),* and 9 of 159 *(5.7)*
		Golimumab (50 mg) + MTX *(159)*	Lupus-like syndromes	0
		Golimumab (100 mg) + MTX *(159)*	Squamous cell carcinoma of the skin *(MTX + placebo)*	1 of 160 *(0.6)*
GO-FORWARD *(Keystone et al. 2009)*	RA	MTX + placebo *(133)*	Skin laceration *(Golimumab (100 mg) + placebo)*	1 of 133 *(0.8)*
		Golimumab (50 mg) + MTX *(89)*	Injection-site reaction *(MTX + placebo, Golimumab (50 mg) + MTX, Golimumab (100 mg) + placebo, Golimumab (100 mg) + MTX)*	24: 4 of 134 *(3)*, 5 of 212 *(2.4)*, 10 of 133 *(7.5)*, 5 of 105 *(4.8)*
		Golimumab (100 mg) + placebo *(133)*	Lupus-like syndromes	0
		Golimumab (100 mg) + MTX *(89)*	Squamous cell carcinoma of the skin *(Golimumab (100 mg) + placebo)*	1 of 133 *(0.8)*
GO-AFTER *(Smolen et al. 2009)*	RA	Placebo *(155)*	Injection-site reaction *(Placebo, Placebo to rescue therapy of 50 mg Golimumab, Golimumab (50 mg), Golimumab (50 mg) to rescue therapy of 100 mg, Golimumab (100 mg))*	36: 6 of 155 *(3.9)*, 3 of 72 *(4.2)*, 9 of 152 *(6)*, 2 of 41 *(4.9)*, 16 of 152 *(10.5)*
		Golimumab (50 mg) *(153)*	Lupus-like syndromes	
		Golimumab (100 mg) *(153)*	Squamous cell carcinoma of the skin *(Golimumab (50 mg))*	1 *(NR)*
				1 of 152 *(0.7)*
Kremer et al. (2010)	RA	Placebo + MTX *(129)*	Injection-site reaction *(Placebo + MTX, Golimumab (All dose groups))* at wk 24 and at wk 48	Wk 24: 27: 7 of 129 *(5.4),* 20 of 513 *(3.9);*
		Golimumab (2 mg/kg) *(128)*		Wk 48: 33: 7 of 129 *(5.4),* 26 of 626 *(4.2)*

Table: (*Continued*)

Study name *(Author and date of publication)*	Treated disease	Treatments	Kind of dermatologic adverse events *(Group)*	Number of dermatologic adverse events
		Golimumab (4 mg/kg) *(129)* Golimumab (2 mg/kg) + MTX *(129)* Golimumab (4 mg/kg) + MTX *(128)*		
GO-REVEAL *(Kavanaugh et al. 2009)*	PA	Placebo *(113)*	Injection-site erythema *(Placebo, Combined Golimumab group (50 and 100 mg))*	13: 3 of 113 *(2.7)*, 10 of 292 *(3.4)*
		Golimumab (50 mg) *(146)* Golimumab (100 mg) *(146)*		
Inman et al. (2008)	AS	Placebo *(78)*	Injection-site reaction *(Placebo, Golimumab (50 mg), Golimumab (50 mg) to rescue therapy of 100 mg, Golimumab (100 mg))*	26: 2 of 77 *(2.6)*, 12 of 138 *(8.7),* 3 of 25 *(12)*, 9 of 140 *(6.4)*
		Golimumab (50 mg) *(138)*	Injection-site erythema *(Golimumab (50 mg), Golimumab (50 mg) to rescue therapy of 100 mg, Golimumab (100 mg))*	16: 5 of 138 *(3.6),* 3 of 25 *(12),* 8 of 140 *(5.7)*
		Golimumab (100 mg) *(140)*		

AS = Ankylosing spondylitis, GO-AFTER = Golimumab After Former anti-tumour necrosis factor alpha Therapy Evaluated in Rheumatoid arthritis, GO-REVEAL = Golimumab-A Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody, MTX = Methotrexate, NR = Not reported, PA = Psoriatic arthritis, RA = Rheumatoid arthritis, wk = week.

and MTX, and 4.05% in all the groups confounded as presented in the Kremer et al. study (no separate dosage groups were given). This percentage was raised in the group of patients treated with placebo with golimumab (50 mg) rescue (4.2%) followed by the group treated with golimumab (100 mg) combined with MTX (6.8%), the group treated with golimumab (50 mg) (7.4%), and the group treated with golimumab (100 mg) *ex equo* with the group treated with golimumab (50 mg) with golimumab (100 mg) rescue (8.5%) (Fig. 1B). Similarly, Zhou et al. (2007) have reported no differences between the placebo group and those treated with golimumab in patients with RA. In the study by Xu et al. (2009) in healthy subjects, injection-site reactions appeared in two cases (2 of 55, 3.6%), and were mild.

All these studies differ from those with the other anti-TNF-α blockers (infliximab, etanercept, and adalimumab), as demonstrated by Moustou et al. (2009). Indeed, these authors found a strong and definite association between these biologic agents and infusion/injection-site reactions. However, these manifestations occur in the first month of therapy and do not decrease afterwards, as was demonstrated in the study of Kremer et al. where injection-site reactions were monitored at both week 24 and week 48. These data were also in agreement with the conclusion of Zeltser et al. (2001) who stated that injection-site reactions were uncommon after one month. For recall injection-site reactions that means that relapses of local reactions as observed in etanercept therapy (Gonzalez-Lopez et al. 2007), were not observed with golimumab therapy.

The evaluation of studies of golimumab showed four reporting injection-site erythema (Fig. 2). These later studies are those of Emery et al. (2009) and Kay et al. (2008) in patients with RA, Kavanaugh et al. (2009) in patients with PA, and Inman et al. (2008) in patients with AS (Table). The highest cumulative percentage of injection-site erythema (considering all groups) occurred in the study by Kay et al. (2008) with RA patients (69.3%, 13.9 ± 3.9, n = 5). After this came the study by Inman et al. (2008) with AS patients (21.3 %, 7.1 ± 2.5, n = 3), the study by Emery et al. (2009) with RA patients (17.8%, 5.9 ± 0.6, n = 3), and finally the study by Kavanaugh et al. (2009) with PA patients (6.1%, 3.1 ± 0.4, n = 2) (Fig. 2A). These differences for RA cannot be explained by the disease itself, and the reason is probably more complicated.

For all dose groups with all diseases confounded, we found that the group of patients treated with golimumab (50 mg) and (100 mg) in the study of Kavanaugh et al. (2009) showed the lowest mean percentage of injection-site erythema (3.4%) (Fig. 2B). Next was the group of patients treated with golimumab (50 mg) (3.6 %), followed by the group treated with golimumab (100 mg) (5.7 %), the group treated with golimumab (50 mg) every 2/4 weeks combined with MTX (6.3%), the group treated with golimumab (100 mg) combined with placebo (7%), the group treated with placebo alone (7.3%), the group treated with golimumab (100 mg) combined with MTX (7.4 %), the group treated with golimumab (50 mg) combined with MTX (9.3%), the group treated with golimumab (50 mg) with golimumab (100 mg) rescue (12%), and finally the group treated with golimumab (100 mg) every week combined with MTX (28.6%) (Fig. 2B). Overall, these results demonstrate that neither golimumab dose, nor the use or not of MTX can clearly modulate injection-site erythema in one direction or the other.

Other dermatologic manifestations in clinical trials with golimumab therapy are mentioned in the Table. The study by Kay et al. (2008) reported the presence of pruritus, pain, induration, burning, hemorrhage, stinging, urticaria, and swelling principally in the groups treated with golimumab. On the other hand, Keystone et al. (2009) were the only group to report skin laceration, in one patient treated with golimumab (100 mg) combined with placebo, which was not significant (0.8%). These findings are in accordance with those for other anti-TNF-α blockers which have been associated with various cutaneous lesions, for example erythema, cutaneous lupus lesions, or vasculitic, urticarial, or purpuric lesions (Hata and Kavanaugh 2006). All these cutaneous lesions disappear after anti-TNF-α therapy is withdrawn (Hata and Kavanaugh 2006).

In this study, neither injection-site reaction nor injection-site erythema were closely associated with golimumab treatment, because higher percentages were also found in placebo-treated groups. Moreover, MTX did not decrease these percentages, demonstrating that MTX cannot improve patient outcomes in respect of the cited injection-site reactions or injection-site

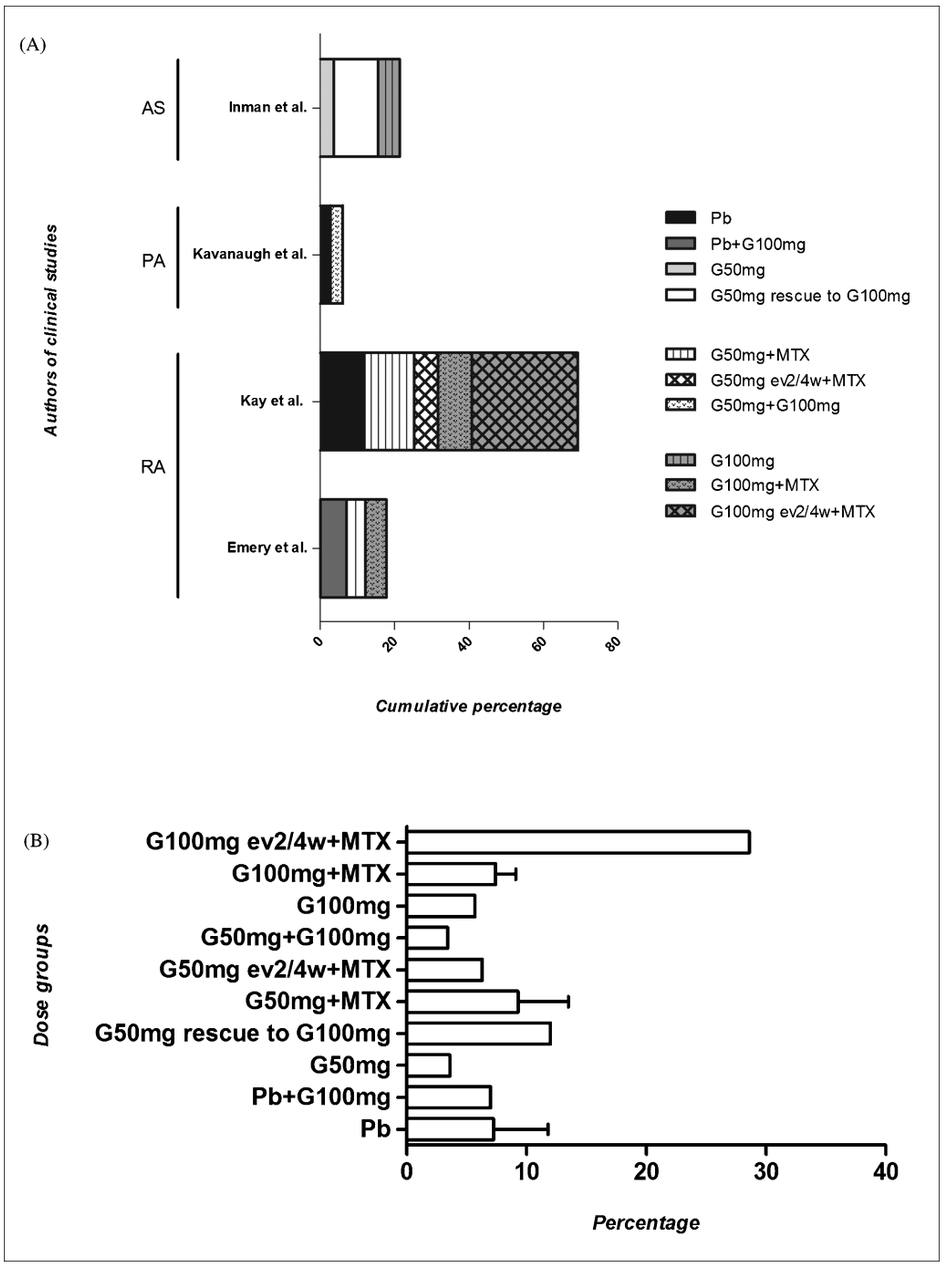

Fig. 2: Injection-site erythema percentage distribution in different clinical studies after golimumab therapy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. (A) Monitored cumulative percentage with their correcponding authors. (B) Mean of monitored percentage ± SEM Abbreviations: AS = Ankylosing spondylitis, ev = every, G = Golimumab, MTX = Methotrexate, PA = Psoriatic arthritis, Pb = Placebo, RA = Rheumatoid arthritis, wk = week

erythema. According to the authors' reports, no patients discontinued their treatment with golimumab due to these dermatologic manifestations, as with other anti-TNF-α blockers such as infliximab (Hata and Kavanaugh 2006).

The frequency of lupus-like syndrome in golimumab trials was not significant, where the relevant data were provided. On the contrary, and as expected, lupus appears not to be associated with high concentrations of autoantibodies, especially anti-nuclear antibodies, after golimumab therapy. However, not all studies on golimumab systematically monitored manifestations of lupus. Only three studies reported the absence of such dermatologic manifestations (Emery et al. 2009; Kay et al. 2008; Keystone et al. 2009). Only the study by Smolen et al. (2009) reported one case of lupus-like syndromes. However, a clear association between golimumab and lupus-like syndromes cannot be confirmed, and needs further studies. These findings remain in opposition to the unambiguous association of lupus with other TNF-α blockers (infliximab, etanercept, and adalimumab) as indicated by Moustou et al. (2009).

The association of dermatologic malignancies with golimumab therapy is not very clearly demonstrated. Indeed, only three cases of squamous cell carcinoma of the skin were reported in the studies of Emery et al. (2009, 0.6%, Keystone et al. (2009, 0.8%), and Smolen et al. (2009, 0.7%) (Zidi et al. 2010). An interesting report is found in the study by Emery et al. (2009) where a confirmed case of malignancy was found in one patient treated only with MTX combined with placebo. Furthermore, the dose of golimumab was not very closely associated with a possible

increase in squamous cell carcinoma of the skin. Indeed, the same number of patients with this malignancy was found with golimumab (50 mg) in the study by Smolen et al. (2009) and with golimumab (100 mg) as in patients treated with placebo in the study by Keystone et al. (2009). All these findings suggest no meaningful association between golimumab treatment and such malignancies.

4. Conclusion

This study of dermatologic manifestations after golimumab treatment clearly indicates discrepancies in the data due to the few studies, and the limited number of patients included. However, we believe that the data presented will be useful, and will be useful for dermatologists for prevention and information. Further research, particularly with increased patient cohorts, may determine whether the risk of dermatologic adverse events is really present after golimumab therapy. Systematic dermatologic screening and further intensive investigations should be performed to reach this goal. Using this strategy, patients' outcomes can be improved by use of the appropriate TNF-α blocker, and by suitable management without stopping treatment.

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