REVIEW

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# Golimumab and immunogenicity? 2010 and beyond

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Immunogenicity is a frequent adverse event observed with biological agents' therapy. Challenges of management in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis treated with golimumab, an anti-TNF-α blocker, include limited generation of antibodies like anti-nuclear, anti-golimumab, and anti-double stranded DNA antibodies. We conducted here a meta-analysis study in order to evaluate and compare the newly generated antibody levels after golimumab therapy. The examination of original clinical trials revealed that their levels were neither higher nor significant. Moreover, no evident associations between the induced-antibodies and lupus-like syndromes and/or infusion site reaction were reported. The reduced patients cohort and the absence of systematic newly generated antibodies follow-up might be implicated in the difficulty to evaluate their risk in delaying diseases therapy, and/or predicting for their worse prognosis. Hence, further studies are required to ascertain the real impact of the induced antibodies after golimumab's therapy.

## 1. Introduction

The use of a drug requires several qualities along with being effective under short-, and long-term conditions. In fact, the drug should be used for patients with different ages, and be associated with non significant adverse effects like fever and diarrhea, and also non classical ones such as immunogenicity, infections and malignancies. In this study, we assessed the immunogenicity of golimumab, a new biological drug recently approved by the Food and Drug Administration (FDA, 2009), across original trials in 2010 and beyond. Golimumab (Trade name: Simponi; CNTO 148; rTNV148B (Food and Drug Administration 2009)) is a human IgG1 kappa monoclonal antibody designed to inhibit TNF-α activity either in its membranous or in its soluble form (Shealy et al. 2007; Food and Drug Administration 2009; Netterwald 2009; Tansey and Szymkowski 2009), in different kinds of pathologies like moderately to severely active rheumatoid arthritis (RA) (Kay et al. 2008; Caporali et al. 2009; Emery et al. 2009; Keystone et al. 2009; Smolen et al. 2009), active psoriatic arthritis (PA) (Kavanaugh et al. 2009; Xu et al. 2009a) and active ankylosing spondylitis (AS) (Inman et al. 2008). This drug is used with methotrexate (MTX) only in patients with RA and not in patients with either PA or AS (Food and Drug Administration 2009).

Generally, golimumab like other TNF-α blockers inhibits the essential function of TNF-α that is host resistance against infection, leading therefore to serious infections like tuberculosis, fungal and opportunistic infections (Hussar 2009). Moreover, golimumab seems to enhance malignancies, nevertheless no clear associations are yet demonstrated (Zidi et al. 2010). It should be stressed, however, that novel studies are urgently needed to clarify the real association between immunogenicity and golimumab therapy. Many discrepancies were detected concerning the systematic follow-up and the dosage of newly generated antibodies after golimumab therapy. To provide more insight into golimumab immunogenicity and to discuss its potential impact on its efficacy, we have focused, in the present study, on the analysis of original studies until March 2010.

## 2. Methods

Original articles were searched in different databases and sources of publications. The searched databases were Cochrane library, EBSCO, HighWire, and PubMed. The search terms were: Golimumab, Simponi, CNTO 148, CNTO148, and CNTO-148. The query was designed to catch all kinds of publications in English and French. Furthermore, the study searched the Food and Drug Administration (FDA) database for their alerts (http://www.fda.gov), and the FDA safety information and adverse events reporting program: the MedWatch (http://www.fda.gov/Safety/MedWatch/default.htm). Publications were gathered until March 2010.

## 3. Results

The study focused on antibodies generated in golimumab therapy in different kinds of diseases: RA, PA and AS. The three kinds of antibodies monitored across the different clinical trials (Table) were anti-nuclear antibodies (ANA), anti-golimumab antibodies (AGA), and anti-double stranded DNA (anti-dsDNA) antibodies (Fig. 1). Bridging immunoassay, the most popular technique used in the detection of these antibodies, allowed us to establish *quasi* head-to-head comparisons. This study has considered every comparison with great caution. Therefore, we studied a range of small groups that differs in the kind of the disease and of the monitored antibodies and also by the therapy

**Table: Incidence rates of anti-nuclear, anti-golimumab, and anti-dsDNA antibodies in clinical trials of golimumab in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis**

| Name of the study *(Authors, date of publication)* | Therapy design | Previous anti-TNF-α blockers therapy | Treated disease | Treatments | Number of patients | Technique for antibodies detection | Kind of generated antibodies *(Groups)* | Number of cases with generated antibodies after golimumab treatment *(%)* |
|---|---|---|---|---|---|---|---|---|
| *(Emery et al., 2009)* | Combination of golimumab + MTX (at a dosage of 10 mg/wk and escalated to 20 mg/wk) | (–) | RA | MTX+ placebo | 160 | NR | –ANA at wk 24 *(MTX+ placebo, Golimumab (100 mg)+ placebo, Golimumab (50 mg) + MTX, Golimumab (100 mg) + MTX)* | –34: 2 of 53 *(3.8)*, 7 of 49 *(14.3)*, 13 of 57 *(22.8)*, 12 of 60 *(20)* |
| | | | | Golimumab (100 mg)+ placebo | 159 | | –Anti-dsDNA | |
| | | | | Golimumab (50 mg) + MTX | 159 | | –AGA *(Golimumab (100 mg)+ placebo, Golimumab (50 mg) + MTX, Golimumab (100 mg) + MTX)* | –0 *(0)* |
| | | | | Golimumab (100 mg) + MTX | 159 | | | –20: 14 of 104 *(13.5)*, 4 of 107 *(3.7)*, 2 of 104 *(1.9)* |
| *(Kay et al., 2008)* | Combination of golimumab + MTX (at a dosage of a least 10 mg/wk for up to 3M) | NR | RA | MTX +placebo | 35 | Bridging immunoassay | –ANA at wk 52 *(MTX+placebo, Golimumab (50 mg) every 4wk + MTX, Golimumab (50 mg) every 2/4 wk+ MTX, Golimumab (100 mg) every 4 wk + MTX, Golimumab (100 mg) every 2/4 wk+ MTX)* | 32: 5of 34 *(17.9)*, 9 of 37 *(27.3)*, 5 of 32 *(16.7)*, 5 of 33 *(16.7)*, 8 of 35 *(23.5)* |
| | | | | Golimumab (50 mg) every 4 wk + MTX | 35 | | –Anti-dsDNA at wk 52 *(MTX+placebo, Golimumab (100 mg) every 2/4 wk+ MTX)* | |
| | | | | Golimumab (50 mg) every 2 wk+ MTX | 34 | | –AGA at wk 48 *(Golimumab (50 mg) every 4 wk + MTX and Golimumab (50 mg) every 2 wk+ MTX groups confounded, Golimumab (100 mg) every 4 wk+ MTX and Golimumab (100 mg) every 2 wk+ MTX groups confounded)* | *–2:* 1 of 34 *(3.6)*, 1 of 35 *(2.9)* |

**Table:** (*Continued*)

| Name of the study *(Authors, date of publication)* | Therapy design | Previous anti-TNF-α blockers therapy | Treated disease | Treatments | Number of patients | Technique for antibodies detection | Kind of generated antibodies *(Groups)* | Number of cases with generated antibodies after golimumab treatment *(%)* |
|---|---|---|---|---|---|---|---|---|
| | | | | Golimumab (100 mg) every 4 wk+ MTX | 34 | | | |
| | | | | Golimumab (100 mg) every 2 wk+ MTX | 34 | | | –7*:* 5 of 107 *(4.6),* 2 of 107 *(1.9)* |
| GO-FORWARD *(Keystone et al., 2009)* | Combination of golimumab + MTX | (–) | RA | MTX+ placebo | 133 | Bridging immunoassay | –ANA at wk 14 *(MTX+ placebo, Golimumab (50 mg) + MTX, Golimumab (100 mg)+ placebo, Golimumab (100 mg) + MTX)* | –NR: NR *(14.9),* NR *(5.7),* NR *(29.3),* NR *(17.9)* |
| | | | | Golimumab (50 mg) + MTX | 89 | | –AGA at wk 24 *(Golimumab (100 mg)+ placebo)* | |
| | | | | Golimumab (100 mg)+ placebo | 133 | | | –5 of 236 *(2.1)* |
| | | | | Golimumab (100 mg) + MTX | 89 | | | |
| *(Kremer et al., 2010)* | Golimumab + stable doses of MTX, NSAIDs, or corticosteroids | (+) | RA | Placebo+MTX | 129 | Bridging immunoassay | –AGA at wk 24 *(Golimumab (2 mg/kg) and Golimumab (4 mg/kg), Golimumab (2 mg/kg)+MTX and Golimumab (4 mg/kg)+MTX)* | –27: 17 of 194 *(9),* 10 of 299 *(3)* |
| | | | | Golimumab (2 mg/kg) | 128 | | –AGA at wk 48 *(NR dose groups)* | |
| | | | | Golimumab (4 mg/kg) | 129 | | | –43 of 613 *(7)* |
| | | | | Golimumab (2 mg/kg)+MTX | 129 | | | |
| | | | | Golimumab (4 mg/kg)+MTX | 128 | | | |
| GO-AFTER *(Smolen et al., 2009)* | Golimumab + stable doses of DMARDs (MTX, sulfasalazine, and hydroxychloroquine: alone or in combination), corticosteroids, and NSAIDs. | (+) | RA | Placebo | 155 | Bridging immunoassay | –ANA at wk 24 *(Placebo, Golimumab (NR dose))* | –14: 2 of NR *(7),* 12 of NR *(7)* |
| | | | | Golimumab (50 mg) | 153 | | –AGA at wk 24 *(Placebo, Golimumab (NR dose groups))* | –8:0 *(0),* 8 of 264 *(3)* |
| | | | | Golimumab (100 mg) | 153 | | | |

**Table:** (*Continued*)

| Name of the study *(Authors, date of publication)* | Therapy design | Previous anti-TNF-α blockers therapy | Treated disease | Treatments | Number of patients | Technique for antibodies detection | Kind of generated antibodies *(Groups)* | Number of cases with generated antibodies after golimumab treatment *(%)* |
|---|---|---|---|---|---|---|---|---|
| *(Zhou et al., 2007)* | Golimumab with intravenous and subcutaneous administration+ stable doses of up to 2 DMARDs (MTX, leflunomide, sulfasalazine, plaquentil, intramuscular gold injections), corticosteroids ≤10 mg/d prednisone equivalent, and/or NSAIDs. | (–) | RA | Placebo | 10 | NR | –ANA *(Placebo, Golimumab (All dose groups))* | –8: 1of 10 *(10),* 7 of 26 *(27)* |
| | | | | Golimumab (0.1 mg/kg) | 3 | | –Anti-dsDNA | –0 *(0)* |
| | | | | Golimumab (0.3 mg/kg) | 3 | | –AGA *(Golimumab (0.1 mg/kg), Golimumab (3 mg/kg), Golimumab (10 mg/kg))* | –3: 1 of 3 *(33),* 1 of 5 *(20),* 1 of 5 *(20)* |
| | | | | Golimumab (1 mg/kg) | 5 | | | |
| | | | | Golimumab (3 mg/kg) | 5 | | | |
| | | | | Golimumab (6 mg/kg) | 5 | | | |
| | | | | Golimumab (10 mg/kg) | 5 | | | |
| GO-REVEAL *(Kavanaugh et al., 2009)* | Golimumab + stable doses of MTX, corticosteroids, and NSAIDs. | (–) | PA | Placebo | 113 | Bridging immunoassay | –AGA *(NR dose groups)* | NR *(4.6)* |
| | | | | Golimumab (50 mg) | 146 | | | |
| | | | | Golimumab (100 mg) | 146 | | | |

**Table:** (*Continued*)

| Name of the study *(Authors, date of publication)* | Therapy design | Previous anti-TNF-α blockers therapy | Treated disease | Treatments | Number of patients | Technique for antibodies detection | Kind of generated antibodies *(Groups)* | Number of cases with generated antibodies after golimumab treatment *(%)* |
|---|---|---|---|---|---|---|---|---|
| *(Xu et al., 2009)* | Golimumab + stable doses of MTX, corticosteroids (Prednisone equivalent ≤10 mg/d), and NSAIDs. | (–) | PA | Placebo | 113 | Bridging immunoassay | –AGA at wk 24 *(NR dose groups)* | 30 *(NR)* |
| | | | | Golimumab (50 mg) | 146 | | | |
| | | | | Golimumab (100 mg) | 146 | | | |
| GO-RAISE *(Inman et al., 2008)* | Golimumab + stable doses of MTX, sulfasalazine, hydroxychloroquine, corticosteroids, and NSAIDs. | (–) | AS | Placebo | 78 | Bridging immunoassay | -AGA at wk 24 *(Golimumab (50 mg), Golimumab (50 mg) to rescue therapy of 100 mg, Golimumab (100 mg))* | 11: 5 of 138 *(3.6)*, 3 of 25 *(12.5)*, 3 of 140 *(2.1)* |
| | | | | Golimumab (50 mg) | 138 | | | |
| | | | | Golimumab (100 mg) | 140 | | | |

AGA = Anti-golimumab antibodies, ANA = Anti-nuclear antibodies, Anti-dsDNA = Anti-double stranded DNA antibodies, AS = Ankylosing spondylitis, DMARDs = Disease-modifying antirheumatic drugs, GO-AFTER = Golimumab After Former anti-tumour necrosis factor alpha Therapy Evaluated in Rheumatoid arthritis, Golimumab for subjects With Active Rheumatoid arthritis Despite MTX, GO-RAISE = Golimumab-A Randomized Study in Ankylosing Spondylitis Subjects of a Novel Anti-TNF monoclonal antibody Injection [Subcutaneous] Given Every Four Weeks, GO-REVEAL = Golimumab-A Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody, M = Month, MTX = Methotrexate, NR = Not reported, NSAIDs = Non-steroidal anti-inflammatory drugs, PA = Psoriatic arthritis, RA = Rheumatoid arthritis, wk = Week, (+) existence of previous therapy with anti-TNF-α blockers, (–) absence of previous therapy with anti-TNF-α blockers.

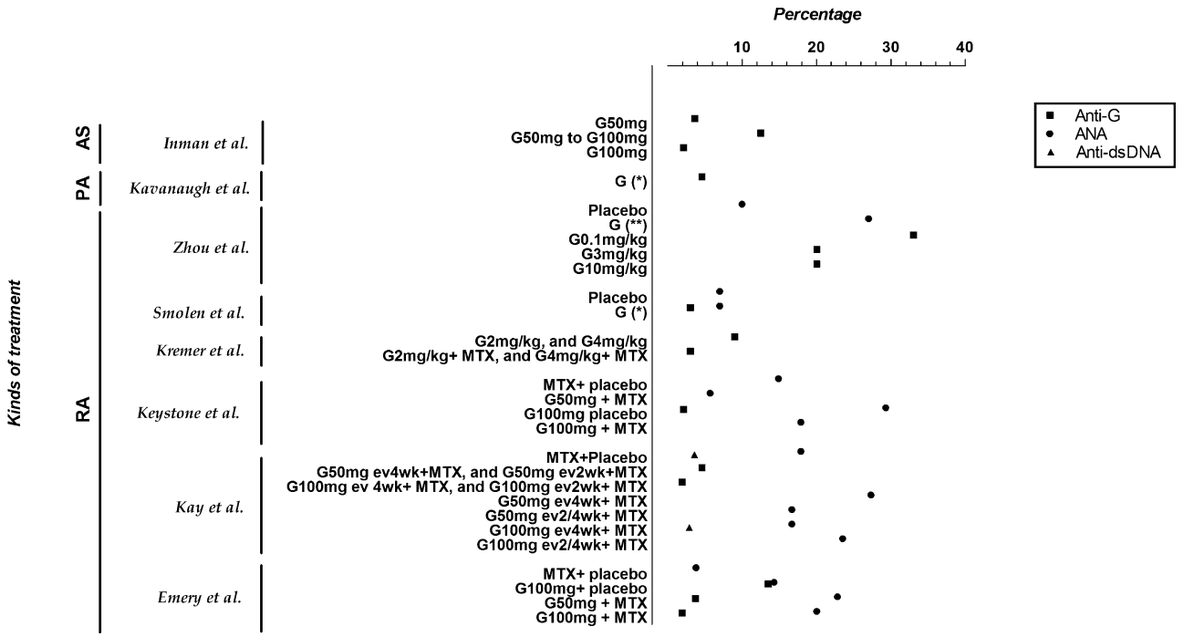


Fig. 1: Anti-nuclear, Anti-dsDNA, and anti-golimumab antibodies distribution in different clinical studies in golimumab thrapy in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis Abbriviations: ANA = Antibodies anti-nuclear antibodies, Anti-dsDNA = Anti-double stranded DNA antibodies, Anti-G=Anti-Golimumab antibodies, AS = Ankylosing spondylitis, G = Golimumab, ev = every, MTX = Methotrexate, PA = Psoriatic arthritis, RA = Rheumatoid arthritis, wk = week, (*) = Not reported dose of golimumab groups, (**) = All golimumab dose group

design (like golimumab dose, use or not of MTX, use or not of previous TNF-α blockers).

In the case of patients with RA treated with golimumab, anti-dsDNA antibodies detection were the less (2.9%, Kay et al. 2008). The percentages of ANA were more enhanced than the percentages of anti-dsDNA (The percentages were situated between 5.7% to 29.3% in Keystone et al. (2009). Importantly, the highest antibodies percentage was attributed to AGA and scaled from 1.9% in the study of Emery et al. (2009) to 33% in the study of Zhou et al. (2007) (Fig. 1). The absence of systematic dosage of these three antibodies does not allow us to compare their percentages concerning other diseases (PA and AS).

### *3.1. Anti-nuclear antibodies*

In the case of RA studies, ANA were explored in 5 out of 6 studies (Fig. 2). The examination of Kay et al. (2008), Emery et al. (2009), and Keystone et al. (2009) studies that used the same golimumab doses (50 and 100 mg), revealed the following results: (1) Patients treated with MTX combined with placebo manifested a small percentage of ANA in the study of Emery et al. (2009, 3.8%) compared to the two other studies where the percentage was 14.9% in the study of Keystone et al. (2009), and 17.9% (Kay et al. 2008). The interesting enhancement of 17% (between Keystone et al. (2009) and Kay et al. (2008) may be attributed to the time of ANA dosage performed in week 14 (Keystone et al. 2009), and in week 52 (Kay et al. 2008); (2) Patients treated with golimumab 50 mg combined with MTX manifested more increased percentages of ANA contrarily to patients treated only with MTX associated to placebo. Indeed, in the study of Keystone et al. (2009), the percentage of ANA was 5.7% whereas it was 22.8% and 27.3% respectively for Emery et al. (2009) and Kay et al. (2008) (3) With 100 mg golimumab, ANA percentage has changed compared with their percentage obtained with 50 mg golimumab (previous groups, see (2)). In fact, we observed an enhancement from golimumab 50 mg to golimumab 100 mg dose in ANA percentage estimated to 68% (Keystone et al. 2009), whereas in both studies of Kay et al. (2008) and Emery et al. (2009), this percentage has decreased to 39% and 12% respectively.

As shown in the Table, the percentage of ANA has not decreased as expected in patients with RA treated with golimumab at doses from 0.1 mg/kg to 10 mg/kg in the study of Zhou et al. (2007). The authors have shown 10% of ANA with placebo group and 27% with golimumab groups (not specified dose groups). This latter percentage is similar that obtained by Kay et al. (with golimumab 50 mg, 27.3%, Kay et al. 2008) suggesting a potential phenomenon of tolerance with golimumab 50 mg. A similar study using doses scaling from 0.1 mg/kg to 50 mg/kg, is still needed to confirm this suggestion.

In the only study that evaluated golimumab efficacy in patients with RA having previously taken other TNF-α blockers (Smolen et al. 2009) (Table), ANA percentage was comparable in patients groups who were taking golimumab or those who were not. Indeed, in the placebo group, and in groups treated with golimumab (not specified dose groups), ANA percentage was 7%. Interestingly, ANA percentage has not increased after multiple "immunizations" with different TNF-α blockers. This result suggested that changing TNF-α blockers in failure cases may probably not have severe consequences in term of immunogenicity.

Concerning ANA detection in patients with other diseases like PA or AS after their treatment with golimumab, nothing was reported. Further studies checking these antibodies are still needed to clarify their production after different golimumab doses.

Lupus-like syndrome manifestations closely related to ANA production were not systematically screened in golimumab studies. Only three studies (Kay et al. 2008; Emery et al. 2009, and Keystone et al. 2009) have shown the absence of lupus in ANA positive patients. Contrarily, Smolen's study reported a case of lupus-like syndrome 3 days after the first dose of golimumab (Smolen et al. 2009). The patient had previously taken other TNF-α blockers suggesting that golimumab therapy is not in close relation with lupus manifestation.

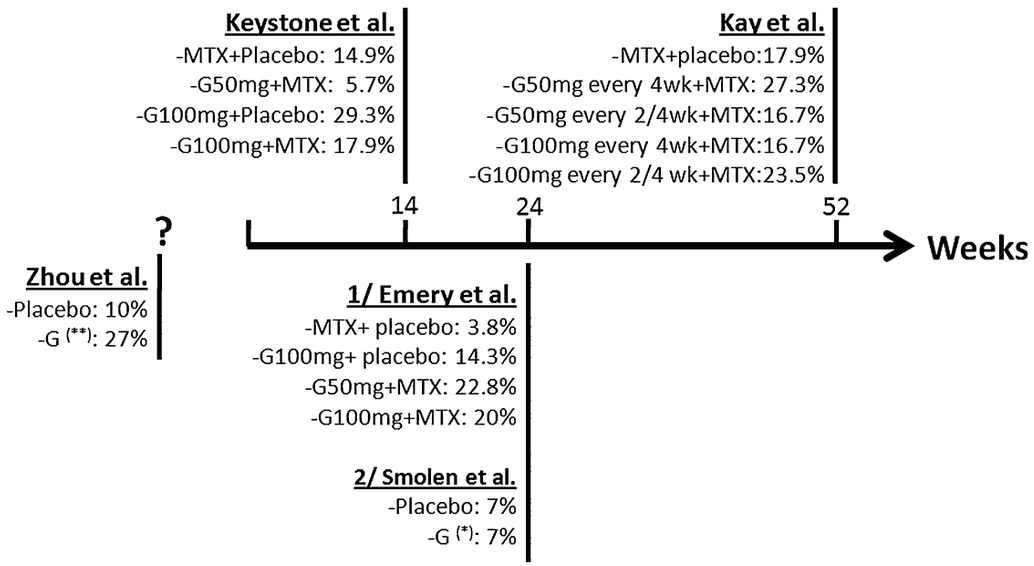


Fig. 2: Chronology and percentage of anti-nuclear antibodies monitored after golimumab therapy in patients with rheumatoid arthritis (Until March 2010) Abbreviations G = Golimumab MTX = Methotrexate wk = Week ? = Not indicated week of dosage (*) = Not reported dose of Golimumab groups (**) = All Golimumab dose groups

### *3.2. Anti-golimumab antibodies*

Several discrepancies were noticed in studies of AGA generation after golimumab therapy. Indeed, the percentage of AGA was not significant because it was under 2% (Kay et al. 2008, Emery et al. 2009). Although, this percentage increased in Zhou's study reaching 33% (Zhou et al. 2007) (Fig. 3). In the FDA report, golimumab (dose not reported) was only associated to 4% of AGA in week 24 (Food and Drug Administration 2009).

We made two cohorts from RA patients treated with golimumab. The first cohort concerns classical doses of golimumab (50 and 100 mg), and the second one concerns golimumab doses scaled from 0.1 mg/kg to 10 mg/kg. Concerning the first cohort: (1) Patients treated with golimumab 100 mg associated to placebo have developed, on the one hand, a relatively high percentage of AGA (13.5%) (Emery et al. 2009), and on the other hand, a low percentage of AGA in Keystone's study (2.1%). One could not compare both studies better because of the lack of information about the technique used in Emery's study (Emery et al. 2009). We could not speculate any false-positive patients based on the technical steps of Emery's study. (2) For patients treated with golimumab 50 mg or 100 mg, a dramatic decrease of AGA compared to Emery et al. (2009) results was observed. This is probably associated with the combination of MTX with golimumab. The treatment with golimumab 50 mg combined with MTX (administrated every 4 weeks, and every 2 and 4 weeks) induced 3.7% and 4.6% of AGA percentage respectively (Kay et al. 2008; Emery et al. 2009). The use of golimumab 100 mg associated with MTX (administrated every 4 weeks, and every 2 and 4 weeks) revealed an AGA percentage equaling 1.9% the study by (Kay et al. 2008; Emery et al. 2009). In Smolen et al. (2009) conducted with patients previously treated with other TNF-α blockers and later with classical doses of golimumab (50 or 100 mg, not specified dose groups), AGA percentage has not increased comparing with studies performed with patients naïve to any TNF-α blocker. Indeed, AGA percentage was estimated to 3% and was not very different from percentages as shown in the previous studies (Kay et al. 2008; Emery et al. 2009).

The second cohort of RA patients that used golimumab doses scaled from 0.1 mg/kg to 10 mg/kg has not developed similar AGA percentages. On the one hand, Kremer et al. (2010) have obtained AGA percentages as Emery et al. (comparable to those determind by 2009) and Kay et al. (2008). They found 9% positive AGA patients after treatment by golimumab 2 mg/kg combined with golimumab 4 mg/kg at week 24. The inclusion of MTX was associated to an AGA percentage decrease to 3% therefore underlining the beneficial role of MTX in RA therapy. On the other hand, the study of Zhou et al. (2007) has interestingly reported an increase in AGA percentage (Fig. 3): 33% with 0.1 mg/kg, and 20% with both 3 mg/kg and 10 mg/kg of golimumab. We speculate that these percentages may be due to the technique itself, but confirmation is still needed.

In the Zhou et al. study, we expected a high injection-site reaction, but unfortunately this information was not reported. The only studies that dealt with this dermatologic manifestation were those of Kay et al. (2008) and Keystone et al. (2009). The first authors reported a mild and not severe injection-site reaction, whereas the second ones reported no positive injection-site reaction in patients with positive AGA.

For PA patients treated with golimumab, only one study can be exploited (Kavanaugh et al. 2009), the percentage of AGA was 4.6% (Fig. 4). However, the study of Xu et al. (2009a) has not reported any exploitable percentage (Table). Studies monitoring AGA levels at long-term are still needed because both studies of Kavanaugh et al. (2009), and Xu et al. (2009a) have explored AGA levels at only short-term (respectively at week 12, and at week 24).

In the case of AS patients treated with golimumab, Inman et al. (2008) reported AGA positive patients when they have not received MTX. The dosage performed at week 24 revealed 3.6% and 2.1% AGA percentages respectively for patients treated with golimumab 50 mg and with golimumab 100 mg. In the same study, 12.5% from a group of patients initially treated with golimumab 50 mg that has rescued to golimumab 100 mg were AGA positive. The highest AGA titer (1/2560) was reported in this latter group.

### *3.3. Anti-double stranded DNA antibodies*

Only three studies performed with RA patients have monitored anti-dsDNA antibodies (Fig. 4). Two studies, with unknown dosage technique, reported no anti-dsDNA (Emery et al. 2009; Zhou et al. 2007). These data were in accordance with those of a controlled phase 3 trial performed with RA, PA, and AS

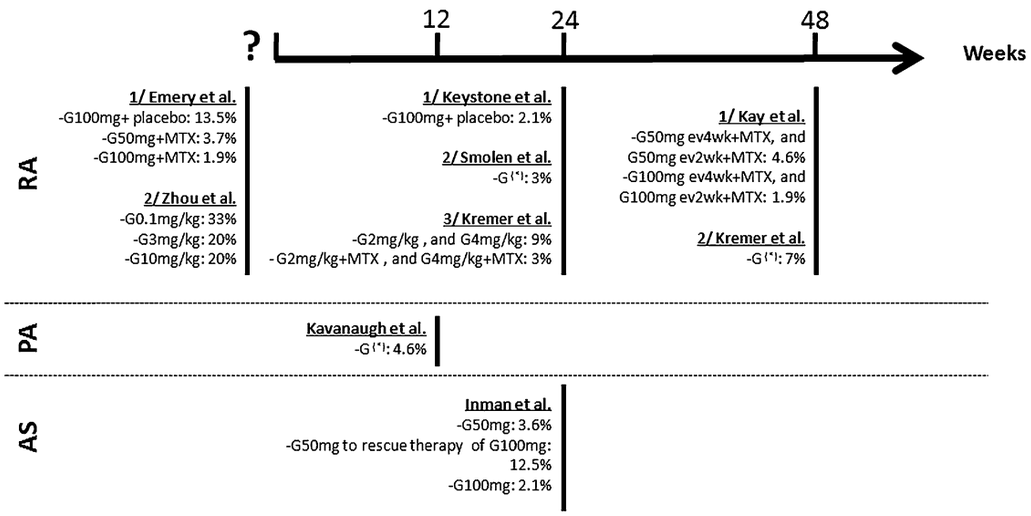


Fig. 3: Chronology and percentage of anti-Golimumab antibodies monitored after golimumab in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis (Until March 2010) Abbreviations AS =ankylosing spondylitis ev = Every G = Golimumab MTX = Methotrexate PA = psoriatic arthrits RA = rheumatoid arthritis wk = week ? = Not indicated week of dosage (*) = Not reported dose of Golimumab groups

through week 14 indicating no association of golimumab with newly generated anti-dsDNA (Food and Drug Administration 2009).

The study of Kay et al. (2008) was the only study reporting anti-dsDNA at week 52 by bridging immunoassay. For patients treated with MTX combined with placebo, or treated with golimumab 100 mg every 2/4 weeks combined with MTX, anti-dsDNA percentages were respectively 3.6% and 2.9%.

## 4. Discussion

Monitoring antibodies generation after anti-TNF-α blockers therapy may help to optimize dose regimens for individual patients, to fulfill risk of adverse events, and to prevent a prolonged use of inappropriate anti-TNF-α blockers (Bendtzen et al. 2006). Certainly, the presence of high autoantibody levels raised against therapeutic antibodies may be associated with drug inefficacy. Indeed, autoantibodies generated in patients with Crohn's disease (CD) after certolizumab therapy demonstrate evident increased drug clearance (Schreiber et al. 2005). Moreover, patients with detectable anti-infliximab antibodies have lower mean serum levels of infliximab *versus* negative anti-infliximab antibodies patients (Wolbink et al. 2006). One recent study demonstrated that ANA and anti-dsDNA generation after TNF-α treatment may act as a marker of forthcoming treatment failure (Pink et al. 2009). Another study supported these findings, in the case of positive AGA patients, that have manifested an increased risk of infusion-reactions and treatment failure (Bendtzen et al. 2006).

Several groups have now suggested and discussed the role of autoantibodies in the decrease of TNF-α blocker efficacy. It was reported that anti-drug antibodies (ADA) may complicate the interpretation of toxicity, pharmacokinetics and pharmacodynamics data (Geng et al. 2005; Koren et al. 2008). Elsewhere, it was reported that ADA may cause adverse events including infusion-reactions, hypersensibility (Geng et al. 2005) and autoimmunity (Shankar et al. 2008). Of considerable intrigue is the result of the study dealing with golimumab in healthy subjects which have presented the same concentration-time profile either with or without AGA (Xu et al. 2009b).

Similar to other TNF-α blockers, golimumab has generated antibodies like ANA, AGA and anti-dsDNA. Golimumab seems to be able to induce ANA percentage more like etanercept than infliximab. Indeed, ANA were found in significant percentages after infliximab therapy in patients with CD (Atzeni et al. 2005), with RA (Alshekaili et al. 2010) and with spondyloarthropathy (Lin et al. 2008). ANA percentages were situated between 34% and 95% in RA patients treated with infliximab, and between 11% and 54% in RA patients treated with etanercept (Valesini et al. 2007). In the same manner, golimumab seems to be able to generate anti-dsDNA (3.6% anti-dsDNA (Kay et al. 2008)) more like etanercept than infliximab or adalimumab. Indeed, in the study of Valesini et al. (2007), conduced with RA patients, anti-dsDNA percentage ranged between 0 and 66% after infliximab therapy, between 0 and 10% after etanercept therapy, and has reached 12.5% after adalimumab therapy.

Usually, anti-dsDNA antibodies isotype was either of IgM (Charles et al. 2000; Ferraro-Peyret et al. 2004; De Rycke et al. 2005), or of both IgM and IgA (Caramaschi et al. 2009) during infliximab therapy in patients with RA, and also in patients with spondyloarthropathy (De Rycke et al. 2003). The isotype role in autoimmune diseases remains unclear, although there are some speculations of the switch from IgM isotype to the pathogenic IgG isotype (Ferraro-Peyret et al. 2004). Unfortunately, there is no information concerning the isotype of anti-dsDNA antibodies generated after golimumab therapy.

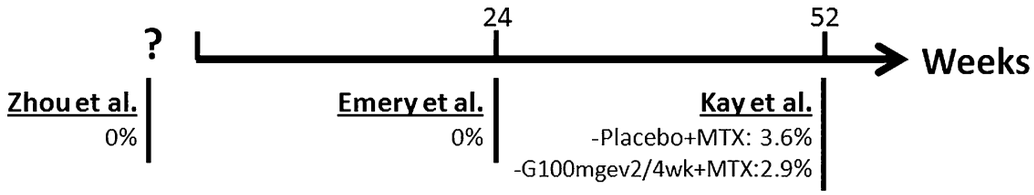


Fig. 4: Chronology and percentage of anti-dsDNA antibodies monitored after golimumab therapy in patients with rheumatoid arthritis (Until March 2010) Abbreviations ev = Every G = Golimumab MTX = Methotrexate wk = week ? = Not indicated week of dosage

Not to be ignored, the newly generated antibodies after anti-TNF-α therapy were influenced, on the one hand by the dose of the drug which may enhance antibody generation and induce tolerance with high TNF-α blocker doses (Wolbink et al. 2006; Valesini et al. 2007), and on the other hand by the use of immunosuppressants like MTX promoting their decrease (Anderson 2005). In this context, Wolbink et al. (2006) suggest that high doses of infliximab may reduce anti-infliximab production by immune tolerance, or alternatively, it could be the result of overdosing the immune system capacity to produce anti-infliximab antibodies.

Although much has been learned, many discrepancies continue to confound the understanding of antibody generation after golimumab therapy. They are closely related to differences in the design of therapy (presence or not of MTX, presence or not of previous treatment with other TNF-α blockers, dose of golimumab and the way of its administration) and in patients themselves (age, sex, weight, underlying disease). Guidance of the technique (like the cut-off of positivity for the antibodies) and its technical handling (Food and Drug Administration 2009) may also explain these discrepancies. In the recent report of Alshekaili et al. (2010), technical approaches for antibody dosage clearly demonstrate anti-dsDNA antibody level disparity. Indeed, in the same patients cohort, different anti-dsDNA antibody levels were obtained when the dosage technique has been changed (enzyme-linked immunosorbent-assay, indirect immunofluorescence, and multiplex bead array) (Alshekaili et al. 2010).

Apart from the dosage techniques previously announced (Alshekaili et al. 2010), there are other techniques designed for autoantibodies detection like farr assay (Valesini et al. 2007), culture-based bioassays, radioimmunoprecipitation assay, quantitative mass spectrometry, surface Plasmon resonance, and immune-PCR assays (Spengler et al. 2009). Currently, each immunoassay should be properly developed and validated before the study begins ensuring a correct autoantibodies follow-up (Shankar et al. 2008). This is a requirement suggested by the FDA that comprises appropriate characterization and correlation with any pharmacological and/or toxicological observations related to a drug (Geng et al. 2005).

The range of autoantibodies recognized after anti-TNF-α therapy encloses also anti-phospholipid, anti-nucleosome, anti-cardiolipin, anti-extractable nuclear antigen antibodies, and anti-histone antibodies (Furst et al. 2008; Wong et al. 2008). After infliximab therapy for example, RA and AS patients developed anti-phospholipid antibodies (Ferraro-Peyret et al. 2004), anti-histone, and CD patients developed anti-cardiolipin antibodies (Atzeni et al. 2005). Nevertheless no significant anti-nucleosome and anti-extractable nuclear antigen antibodies were reported in RA or in spondyloarthropathy patients after infliximab therapy (De Rycke et al. 2003). Even though the anti-cardiolipin antibodies were detected in RA patients treated with etanercept (Ferraccioli et al. 2002), they have not been detected in RA patients treated with adalimumab in a one-year prospective study (Atzeni et al. 2006). Concerning golimumab, it is likely that the currently known set of announced autoantibodies is not yet complete.

The mechanisms of autoantibody generation remain not well-characterized. The disease itself seems not to be correlated to this generation because ANA, and anti-dsDNA were found in RA patients and also in spondyloarthritis patients (Valesini et al. 2007). The induction of autoantibodies could be due to humoral autoimmunity promotion by the inhibition of cytotoxic T lymphocytes induction that normally suppresses autoreactive B lymphocytes action (Via et al. 2001). The potential implication of anti-TNF-α binding to transmembranous TNF-α was proposed being in the origin of anti-dsDNA development through the enhancement of autoantigens, after apoptotic death (Charles et al. 2000). In addition, the reduction of C-reactive protein (CRP) serum level after anti-TNF-α treatment may deregulate the clearance of apoptotic debris and nuclear material (Gershow et al. 2000; Atzeni et al. 2005) by a similar mechanism as do the murine analog of human CRP that is the serum amyloid P (Bickerstaff et al. 1999). It was also hypothesized that other factors may be implicated in autoantibodies generation like infections and the interleukin-10 (Caramaschi et al. 2006).

Further investigations will be important to clarify the origin of the newly generated autoantibodies, their impact, and their association with dermatologic manifestations like lupus-like syndromes, or infusion-site reactions because of studies' huge disparities. Indeed, some studies established that ANA and anti-dsDNA were neither associated with other lupus-related antibodies, nor with lupus-like syndromes, but proposed close patients monitoring (Debandt et al. 2003; Valesini et al. 2007). Moreover, Aringer et al. (2007) reported the increase of autoantibodies raised against nuclear antigens and phospholipids in systematic lupus erythematosus patients treated with infliximab. However, they have not associated these transient manifestations with disease flares (Aringer et al. 2007). Also, De Rycke et al. (2003) state that a real association between anti-TNF-α treatment and lupus-like syndromes is still difficult. Indeed, it was not possible to clearly prove that these symptoms are either related to anti-TNF-α therapy or to the underlying disease (De Rycke et al. 2003). Also, we cannot We cannot also exclude the implication of other drugs being taken concurrently, or the coincident development during anti-TNF-α therapy (De Rycke et al. 2003).

Differently other studies report an association between anti-TNF-α and autoimmune diseases. One study proposed that RA patients receiving anti-TNF-α blockers may develop glomerulonephritis after induction of nephropathy or *de novo* autoimmune disorders (Stokes et al. 2005). In fact, one patient has developed IgG anti-cardiolipin antibodies that may contribute to vascular lesions (Stockes et al. 2005). Another study in a patient with RA treated with anti-TNF-α therapy, reported the first lupus nephritis case which developed a fast and progressive renal failure (Piccolo et al. 2008). A high prevalence of anti-dsDNA was also reported in drug-induced lupus erythematous case reports due to TNF-α blockers (Costa et al. 2008). Moreover, Comby et al. (2006) extends that the detection of autoantibodies (comprising ANA, anti-dsDNA, and anti-single stranded DNA) may announce lupus-like syndromes and/or anaphylactoid and skin symptoms in patients with active RA after infliximab therapy. Similarly, the impact of etanercept in unmasking pre-existing lupus-like disease was reported in patients with RA (Cairns et al. 2002).

As described in this meta-analysis study, monitoring only three kinds of newly generated antibodies (ANA, anti-dsDNA, and AGA) in golimumab studies indicates evidently incomplete data. Results, reviewed here, suggest information gaps across these studies concerning essentially: (1) kinds of antibodies systematically monitored. Moreover, their dosage timing was not uniform across studies that enhances the difficulty to correctly analyze data, to make easy head-to-head comparisons, or to prevent eventual prolonged use of golimumab; (2) newly generated antibodies isotype that might be helpful to foresee eventual lupus-like syndromes and/or infusion-site reactions, and to rapidly manage patients; (3) the used technique for antibodies detection; and (4) the controls with MTX alone, to avoid the bias of antibodies spontaneously generated under MTX. Further studies using larger cohorts of patients remain mandatory with the challenge to ascertain previous conclusions, to complete missed information, to answer deeply the raised questions,

and to fill the enlarged gap studies rarity related to golimumab immunogenicity.

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