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par

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La réponse aux anti-TNF dans la polyarthrite rhumatoïde : Analyse poolée de données individuelles patients d'essais contrôlés randomisés

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
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si j'y manque.

RESUME

La réponse aux anti-TNF dans la polyarthrite rhumatoïde : Analyse poolée de données individuelles patients d'essais contrôlés randomisés

INTRODUCTION : La réponse aux anti-TNF dans la polyarthrite rhumatoïde (PR) est hétérogène. L'objectif de cette étude était d'identifier des sous-groupes de patients répondant davantage aux anti-TNF.

METHODE : Les données individuelles patients de 29 essais contrôlés randomisés (ECR) évaluant l'efficacité d'un anti-TNF par rapport à un placebo ou à un traitement de fond conventionnel ont été obtenues. La réponse au traitement a été étudiée dans les sous-groupes d'intérêt suivants : statut tabagique, activité physique, genre, âge, IMC, profil d'auto-anticorps, durée d'évolution, forte activité initiale de la maladie. Le critère de jugement principal de réponse choisi était la différence moyenne du ΔDAS28(CRP) à 3 ou 6 mois. Les critères secondaires étaient la différence moyenne de DAS28(CRP) à 3 ou 6 mois et l'Odds ratio de la réponse EULAR à 3 ou 6 mois. Les données agrégées de ces ECR ont été poolées par la méthode de Mantel-Haenszel en utilisant des modèles à effets aléatoires. Une méta régression linéaire a aussi été réalisée séparément sur 2 plateformes de partage données.

RESULTATS : Les données individuelles de 11617 patients de 29 ECR ont été analysées. A 3 ou 6 mois, un taux de non réponse significativement plus important a été observé chez les patients obèses (OR 0,52 contre 0,36 pour les non-obèses ; p=0,01). Dans un modèle de régression multivarié effectué sur 7457 patients, les patients traités par anti-TNF avaient un DAS28(CRP) final diminué de 0,02 pour chaque année d'évolution de la maladie (p<0,001) et un DAS28(CRP) final diminué de 0,21 pour les patients ayant un DAS28(CRP) initial >=5,1 (p=0,05).

CONCLUSION : Dans la PR, les patients répondant davantage aux anti TNF sont ceux étant non-obèses, ayant une durée d'évolution de la maladie importante, et une forte activité initiale de la maladie.

Mots clés : polyarthrite rhumatoïde – anti-TNF – réponse au traitement — sous-groupe – données individuelles patients.

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LISTE DES ABREVIATIONS

ACR	American College of Rheumatology
ADA	Adalimumab
ACPA	Anti-citrullinated protein antibodies
AINS	Anti-inflammatoire non stéroïdien
CCP	Cyclic Citrullinated Peptide
CDAI	Clinical Disease Activity Index
CRP	C-reactive protein
csDMARDs	Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs
CZP	Certolizumab-pegol
DAS28	Disease Activity Score on 28 joints
DMARD	Disease-modifying antirheumatic drugs
ECR	Essai contrôlé randomisé
EIRA	Epidemiological Investigation of Rheumatoid Arthritis
ESR	Erythrocyte Sedimentation Rate
ETN	Etanercept
EULAR	European League against Rheumatism
FR	Facteur Rhumatoïde
GOL	Golimumab
HAQ	Health Assessment Questionnaire
INF	Infliximab
IMC	Indice de masse corporelle
IPD	Individual Patient Data
LDA	Low Disease Activity
MIDRA	Meta-analysis on the Influence of Demographic factors on anti-TNF in RA
NAD	Nombre d'articulation douloureuse
NAG	Nombre d'articulation gonflée
OR	Odds ratio
PR	Polyarthrite Rhumatoïde
PGA	Patient Global Assessment : Evaluation activité de la maladie par le patient
PROSPERO	Prospective Register of Systematic Reviews
SD	Standard Deviation
SDAI	Simplified Disease Activity Index
TNF-alpha	Tumor Necrosis Factor-alpha
tsDMARDs	Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs
UCB	Union chimique belge
VS	Vitesse de sédimentation

SOMMAIRE

TABLE DES ILLUSTRATIONS

Résumé général du travail de thèse

I- Introduction

1-Polyarthrite rhumatoïde

La polyarthrite rhumatoïde (PR) est le rhumatisme inflammatoire chronique le plus sévère et le plus fréquent, touchant 0,3 à 1% de la population générale (1), ce qui représenterait environ 200000 patients en France (2). Elle peut survenir à tout âge mais débute habituellement autour de cinquante ans avec une prédominance féminine avant 60 ans. Le tableau clinique initial est souvent celui d'une polyarthrite bilatérale et symétrique évoluant sur un mode chronique (>6semaines), caractérisée par des douleurs et gonflements articulaires le plus souvent localisées aux poignets, aux articulations métacarpo-phalangiennes et interphalangiennes proximales en respectant les interphalangiennes distales (3). Le clinicien peut s'appuyer sur les critères ACR EULAR 2010 pour en poser le diagnostic (4).

Le score DAS28 est l'outil le plus couramment utilisé pour évaluer l'activité d'une polyarthrite rhumatoïde. C'est un score composite prenant en compte l'inflammation sanguine (VS ou CRP), l'évaluation globale de la maladie par le patient, et le nombre d'articulation douloureuse et gonflée. L'indice permet de classer l'activité de la maladie en activité forte pour un DAS28(VS) supérieur à 5,1 ; activité modérée pour un DAS28(VS) entre 5,1 et 3,2 ; faible activité pour un DAS28(VS) entre 3,2 et 2,6 ; rémission pour un DAS28(VS) inférieur à 2,6.

La polyarthrite rhumatoïde est une maladie multifactorielle, de cause inconnue. Les éléments scientifiques actuels suggèrent que la PR serait la conséquence d'une combinaison initiale d'évènements déclencheurs environnementaux : tabac (5) (6), changement dans le microbiote buccal et intestinal (7), se produisant sur un terrain génétique prédisposé, comme en atteste les groupes HLADR4 et HLADR1 plus souvent retrouvés chez ces patients. Ces événements seraient responsable d'une brèche dans la tolérance immunitaire, menant à une prolifération inappropriée des cellules de l'immunité et la production d'autoanticorps qui stimulerait et maintiendrait une cascade inflammatoire dans la membrane synoviale à travers des cytokines dont le facteur de nécrose tumorale (TNF) (8). Etant donnée l'importance du TNF dans la physiopathologie des maladies inflammatoires et dans la polyarthrite rhumatoïde, plusieurs molécules ayant pour cible cette cytokine ont été développées et ont reçu une autorisation de mise sur le marché.

2-Anti TNF

Cinq anti-TNF sont disponibles pour traiter les patients atteint de polyarthrite rhumatoïde : un récepteur soluble du TNF (l'étanercept) et quatre anticorps monoclonaux (l'adalimumab, le certolizumab, le golimumab et l'infliximab).
Ces molécules font partie des traitements de fond, les DMARDs (Disease Modifying Anti-Rheumatic Drug), qui induisent une amélioration clinique, fonctionnelle et structurale dans l'évolution de la maladie.

On différencie actuellement :

- Les traitements conventionnels csDMARD (conventional synthetic DMARD) : méthotrexate, léflunomide, salazopyrine, hydroxychloroquine.
- Et, les traitements ciblés, en différenciant :
    - Les tsDMARD (targeted synthetic DMARD) obtenus par synthèse chimique : baricitinib, tofacitinib, upadacitinib.
    - Et les bDMARD, obtenus à partir d'une cellule génétiquement modifiée ou d'un organisme vivant :
        - Les anti-TNF
        - Les anti-interleukine 6
        - Le modulateur de la co-stimulation des lymphocytes T (Abatacept)
        - Le Rituximab

Ces traitements de fond sont à différencier des traitements symptomatiques comme les AINS ou les corticoïdes. D'après les recommandations françaises et européennes (9), les anti-TNF sont actuellement des traitements de fond de seconde ligne. En première intention, le méthotrexate reste le traitement de fond de référence. En 2ème ligne, et en présence de facteurs de mauvais pronostic (taux élevé de facteur rhumatoïde et/ou anti-CCP, activité importante de la maladie, atteinte structurale précoce, échec de deux csDMARDs), l'ajout au méthotrexate d'une thérapie ciblée peut être proposée.

II-Le rationnel

Dans la stratégie treat-to-target (9), lorsque la rémission ou à défaut une faible activité de la maladie ne sont pas atteintes à 6 mois pour la première thérapie ciblée, il est conseillé d'en essayer une autre avec une réévaluation de l'efficacité là encore dans les 3 à 6 mois jusqu'à trouver le traitement permettant d'atteindre cet objectif. Bien qu'efficace, cette méthode de

traitement par « trial and error », pourrait être affinée par la recherche de facteurs prédictifs de réponse au traitement avant son initiation. Une prise en charge personnalisée permettrait ainsi de réduire la survenue de dommages articulaires et de diminuer les coûts pour le système de santé (10) en prenant en charge d'éventuels facteurs modifiables qui pourraient intervenir dans la réponse au traitement.

Des facteurs ont été décrits comme étant associés à une moindre réponse aux anti-TNF, tels que le tabagisme (11) (12) (13) (14), le sexe féminin (11) (15) (16), un âge avancé (17) (18), l'obésité (19), la présence de facteur rhumatoïde et d'anticorps anti-CCP (20), une longue durée de la maladie avant le début du traitement (16), une forte activité initiale de la maladie (21) (22) (23) (24), avec cependant des résultats contradictoires retrouvés dans la littérature pour certains de ces facteurs (21) (22) (25).

C'est dans ce contexte, qu'est né en 2016 le projet MIDRA, une méta-analyse ayant pour objectif d'étudier l'influence des facteurs démographiques, environnementaux et liés à la maladie dans la réponse aux anti-TNF dans la polyarthrite rhumatoïde.

III- Le projet MIDRA

1-Introduction

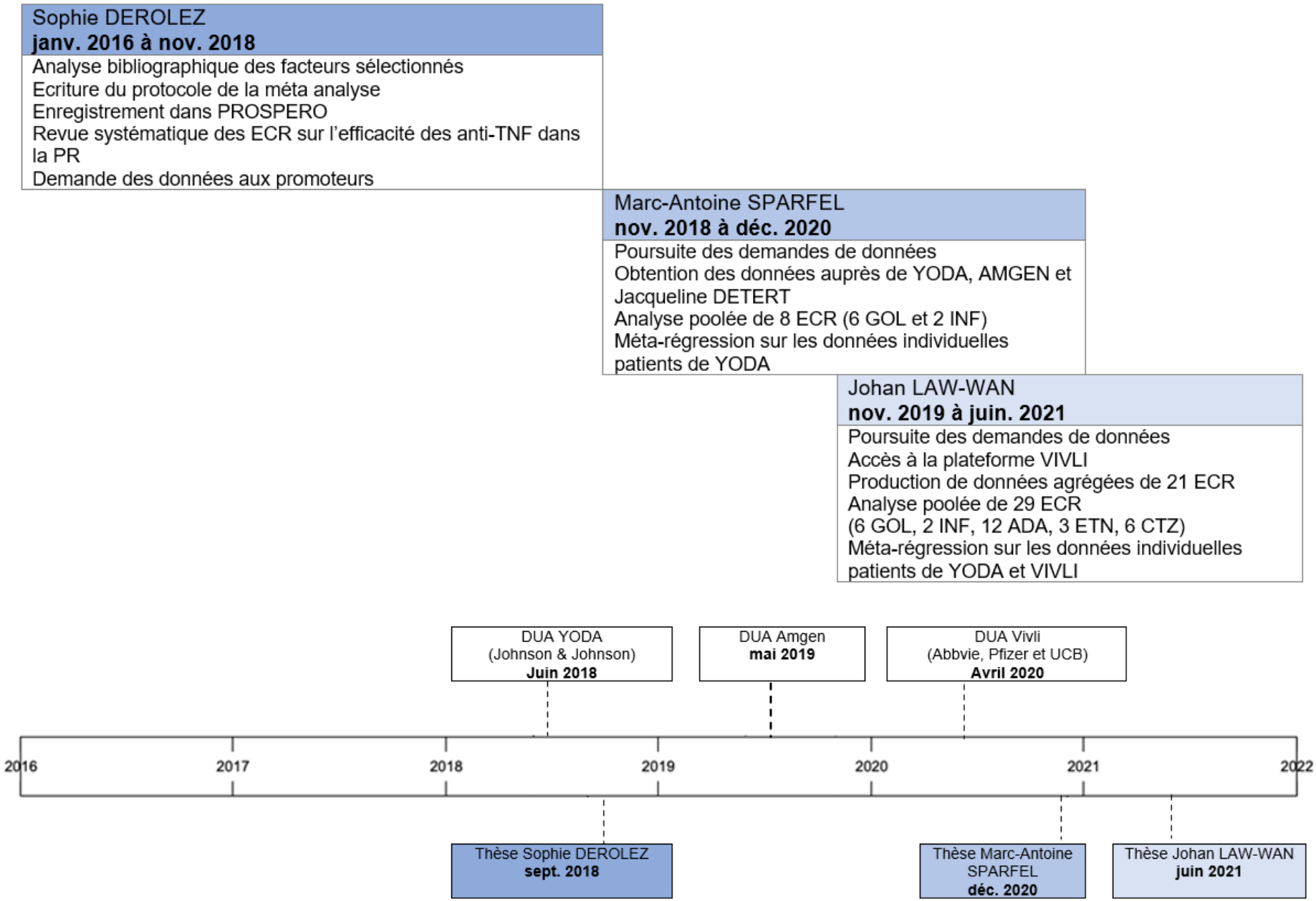
Ce travail de thèse, qui constitue l'aboutissement du projet MIDRA, s'est appuyé sur les travaux réalisés par deux anciens DES de rhumatologie de la Faculté de Médecine de Tours.

Dans le cadre de sa thèse de médecine, le Dr Sophie DEROLEZ a réalisé de janvier 2016 à novembre 2018 une revue systématique des essais cliniques randomisés évaluant l'efficacité d'un anti-TNF versus placebo ou un traitement de fond conventionnel dans la PR. Après avoir constaté l'absence de résultats publiés concernant l'efficacité des anti-TNF dans les sous-groupes souhaités (statut tabagique, activité physique, genre, âge, IMC, profil d'auto-anticorps, durée de la maladie, forte activité initiale de la maladie), le Dr DEROLEZ a entrepris des demandes auprès de différents auteurs et promoteurs des essais cliniques afin de récupérer les données concernant la réponse aux anti-TNF par sous-groupe d'intérêt et de les combiner dans une méta-analyse. En raison des délais et des difficultés à obtenir ces données, le Dr DEROLEZ n'a pu terminer le projet seule.

Le Dr Marc-Antoine SPARFEL, de novembre 2018 à décembre 2020, a poursuivi les demandes d'obtention des données, puis en parallèle a réalisé une première analyse poolée de 8 essais clinique (6 golimumab et 2 infliximab) obtenus via la plateforme YODA (The Yale University Open Data Access). Une méta régression a également été réalisé sur cette plateforme. Ce travail a été soutenu le 4 décembre 2020 dans le cadre de sa thèse de médecine et présenté au congrès de l'EULAR 2021.

Mes objectifs en participant au projet MIDRA à partir de décembre 2019, ont consisté à poursuivre l'obtention des données individuelles de patients issus des études sélectionnées (11 Adalimumab, 1 Etanercept, et 6 Certolizumab), de réaliser une analyse en sous-groupe de 21 études, puis une analyse poolée regroupant ces données agrégées avec les 8 réalisées par le Dr SPARFEL. J'ai pu par la suite réaliser deux méta-régressions sur les plateformes Vivli et YODA afin d'étayer les résultats.

Figure 1 : Chronologie du travail de thèse



2-Obtention des données individuelles patients

J'ai pu participer à l'obtention des données individuelles patients de 18 études auprès de la plateforme de partage de données Vivli (11 Adalimumab, 1 Etanercept et 6 Certolizumab) (26). Il s'agit d'une organisation américaine à but non lucratif, lancée en 2018, et regroupant actuellement 34 membres dont Abbvie, Pfizer et UCB. Ses objectifs sont de collecter les données individuelles de patients issues d'une multitude d'essais clinique et de les mettre à disposition du plus grand nombre (data sharing).

Cette obtention n'a été possible qu'après signature d'un accord d'utilisation des données (Data Use Agreement) entre l'Université de Tours et Vivli : document signé le 09 avril 2020. Ce processus, initié en décembre 2018 par le Dr SPARFEL et dont j'ai repris le relais à partir de décembre 2019, a nécessité de nombreux échanges par mails, visioconférences avec les équipes de Vivli et le Service Partenariats, Innovations et Valorisation de l'Université de Tours (Madame Louise TERRAY).

3- Exploitation des données individuelles patients

J'ai débuté l'exploitation des données provenant de Vivli en septembre 2020, via la connexion à un ordinateur à distance. Pour des raisons de confidentialité et de droits d'auteur, il ne nous était pas permis de télécharger directement les données individuelles de patients : seuls des données agrégées pouvaient être exportées de la plateforme après vérification par Vivli.

La première étape a consisté à extraire les informations souhaitées à partir des données fournies par Vivli, lesquelles étaient dispatchées dans des dizaines de sous fichiers et classés différemment selon les laboratoires pharmaceutiques. Ce travail d'extraction a été réalisé à l'aide du logiciel R studio (R version 3.6.3). Je me suis aidé pour cela des fichiers de programmation R markdown (.rmd) de la plateforme YODA créés par le Dr SPARFEL. L'objectif était de créer pour chaque étude, un tableau de données où chaque ligne représentait un patient, et chaque colonne ses caractéristiques cliniques et biologiques : statut tabagique, activité physique, genre, âge, IMC, statut immunologique pour les facteurs rhumatoïde/anti-CCP, durée d'évolution de la maladie, activité de la maladie initialement puis au moment de l'évaluation. Certains de ces critères ont parfois dues être calculés à partir des données disponibles : IMC calculé à partir du poids et de la taille, nombre d'articulation douloureuse ou gonflée calculé à partir du statut douloureux ou gonflé des 28 articulations d'intérêt évaluées

séparément, réponse EULAR calculée à partir du DAS28(VS) final et l'amélioration du DAS28(VS) (Figure 2).

- Les patient bons répondeurs sont ceux ayant un DAS28(VS) final inférieur ou égal à 3,2 et une amélioration du DAS28(VS) par rapport au niveau de base d'au moins 1,2.
- Les non-répondeurs sont ceux qui ont un DAS28(VS) final supérieur à 5,1 et une amélioration du DAS28(VS) par rapport au niveau de base inférieure ou égale à 1,2. Les patients ayant une amélioration du DAS28(VS) par rapport au niveau de base inférieur ou égale à 0,6 sont également classés comme non répondeurs.
- Les répondeurs modérés sont ceux qui ne remplissent pas les critères des deux groupes précédents.

Figure 2 Critères de réponses EULAR dans la polyarthrite rhumatoïde

ΔDAS28(VS) *(Difference entre DAS28(VS) final et DAS28(VS) initial)*			**DAS28(VS) final**
< -1,2	< -0,6 - ≥ -1,2	≥-0,6	
		Non réponse	> 5,1
	Réponse moyenne		≤ 5,1 - > 3,2
Bonne réponse			≤ 3,2

La seconde étape a consisté à produire des données agrégées de 21 études (18 provenant de Vivli, 2 provenant d'AMGEN et une provenant du Dr Jacqueline DETERT), en calculant pour chaque sous-groupe dans chaque étude, le nombre de patients bon répondeurs EULAR, non répondeurs EULAR, la moyenne du DAS28(CRP) final et la moyenne du ΔDAS28(CRP) dans les groupes traitement et placebo (Figure 3).

La dernière étape a consisté à combiner les données agrégées de 29 études (8 produites par le Dr SPARFEL et 21 par moi-même) afin de calculer des odds-ratio poolés de bonne réponse au traitement, des différences moyennes poolées de ΔDAS28(CRP) et de DAS28 finaux entre anti-TNF et placebo dans les sous-groupes d'intérêt, à partir du poids de chaque étude dans l'analyse. Ceci dans l'objectif de mettre en évidence d'éventuelles différences de réponse au traitement entre sous-groupes.

Figure 3 : Principales étapes de l'exploitation des données individuelles de patients.

1/Données individuelles de patients

Etude 1

Patients	Genre	Age	Bras	Réponse EULAR	DAS28(CRP) final
XVA	H	49	ADA	Non	5,2
BJI	F	67	ADA	Bonne	1,3
VOF	F	55	PLB	Bonne	1,5

Etude 2

Patients	Genre	Age	Bras	Réponse EULAR	DAS28(CRP) final
MRG	H	60	ETN	Bonne	1,5
KTZ	F	47	ETN	Bonne	1,8
LPW	F	58	PLB	Non	5,2

2/Données agrégées

Réponse en fonction du genre

Etudes	Bras	Genre	Nombre de Bon répondeurs EULAR	Moyenne DAS28(CRP) finale
1	Anti-TNF	H		
1	Anti-TNF	F		
1	Placebo	H		
1	Placebo	F		
2	Anti-TNF	H		
2	Anti-TNF	F		
2	Placebo	H		
2	Placebo	F		

Réponse en fonction de l'âge

Etudes	Bras	Age	Nombre de Bon répondeurs EULAR	Moyenne DAS28(CRP) finale
1	Anti-TNF	>50 ans		
1	Anti-TNF	<50 ans		
1	Placebo	>50 ans		
1	Placebo	<50 ans		
2	Anti-TNF	>50 ans		
2	Anti-TNF	<50 ans		
2	Placebo	>50 ans		
2	Placebo	<50 ans		

3/Analyse poolée

Association entre anti-TNF vs placebo et bonne réponse EULAR

Genre	Odds-ratio	Poids de l'étude (%)
Hommes		
Etude 1		
Etude 2		
Poolé		
Femmes		
Etude 1		
Etude 2		
Poolé		

Différence moyenne de DAS28 finale entre anti-TNF et placebo

Age	Différence moyenne	Poids de l'étude (%)
>50 ans		
Etude 1		
Etude 2		
Poolée		
<50 ans		
Etude 1		
Etude 2		
Poolée		

4- Méta régression linéaire

Afin de confirmer et affiner ces résultats, nous avons effectué une méta-régression linéaire sur les données individuelles de patients provenant des plateformes YODA et Vivli séparément.

Nous avons ainsi cherché à établir une relation linéaire entre le DAS28(CRP) final et chacune des variables cliniques et biologiques collectées, dans le but d'identifier des facteurs de bons ou mauvais pronostics sur le DAS28(CRP) final, mais surtout de rechercher d'éventuelles interactions entre le traitement et ces variables sur le DAS28(CRP) final.

L'article rapportant les résultats de l'analyse poolée et de la méta régression linéaire est présentée comme travail de thèse.

Impact of clinical and biological baseline characteristics on response to TNF inhibitors in Rheumatoid Arthritis: An Individual Patient Data based analysis of Randomized Controlled Trials

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Abstract

Objective: Response to TNF inhibitors in rheumatoid arthritis (RA) is highly heterogeneous. Our aim was to identify patients characteristics associated with responsiveness to TNF inhibitors in RA.

Material and methods: Individual patients data from 29 randomized controlled trials evaluating the efficacy of a TNF inhibitors versus placebo or conventional therapy were obtained. Response to treatment was assessed in subgroups according to the following baseline characteristics : smoking status, physical activity, gender, age, Body Mass Index (BMI), autoantibody profile, disease duration, high initial disease activity defined by DAS28(CRP)>5.1. The primary outcome was the between-group difference in ΔDAS28(CRP) at 3 or 6 months. The secondary endpoints were the between-group differences in DAS28(CRP) at 3 or 6 months and the between-group odds ratio of EULAR response at 3 or 6 months. Data from each study were then pooled by the Mantel-Haenszel method using a random effects model. A linear meta-regression was also carried out on two data-sharing platforms separately to support the results.

Results: Individual data of 11,617 patients from 29 RCTs were analyzed. At 3 or 6 months, a significantly higher EULAR non-response rate was observed in obese patients (OR 0.52 versus 0.36 for non-obese; p=0.01). A multivariate regression model performed on 7,457 patients indicated that patients treated by TNF inhibitors had a final DAS28(CRP) decreased by 0.02 for each year of disease duration (p<0.001), and a 0.21 decreased for patients with a baseline DAS28(CRP)>=5.1 (p<0.001).

Conclusion: In RA, patients who are more responsive to TNF inhibitors are those who are non-obese, have a long disease duration, and a high initial disease activity.

Keywords: rheumatoid arthritis, disease activity, TNF inhibitors, demographic factors, disease-related factors, individual patient data meta-analysis, subgroup analysis

Introduction

Rheumatoid arthritis (RA) is the most common chronic systemic autoimmune disease with a prevalence of 0.3 to 1% (1). Despite considerable progress in the knowledge of its pathogenesis (8) (27) and therapeutic management, disease remission or low disease activity (LDA) (9) is not obtained in all patients. TNF inhibitors were first biologic agents available and are still widely used in patients with inadequate response to conventional disease-modifying antirheumatic drugs (csDMARDs). However, approximately one-third of patients with RA respond insufficiently to TNF inhibitors (28) (29).

The reasons behind the heterogeneity in response remains unclear. Several studies have suggested the role of immunization towards the drug to explain this variability (30) (31) (32). Another explanation could be the pathogenesis, clinical and biological disparities between RA patients. Analysis of the synovial tissues of RA patients has revealed differences in cell infiltration, cytokine or gene expression for patients initially presenting the same clinical characteristics (33) (34), suggesting the possibility of different inflammatory pathways across patients.

Demographic, disease-related and environmental factors could contribute to the variability in clinical response to TNF inhibitors. Some factors have been associated with a poor response such as smoking (11) (12) (13) (14), female gender (11) (15) (16), older age (17) (18), obesity (19), presence of rheumatoid factor and anti-citrullinated peptide antibodies (20), long disease duration (16), high disease activity (21) (22) (23) (24), with conflicting results, though. (21) (22) (25). Available data are sparse on the role of physical activity in the response to TNF inhibitors. Physical actity seems to decrease fatigue (35), improve quality of life (36) (37)but does not seem to decrease inflammation parameters, as such (38). We therefore aimed to study the influence of these factors on the effect of TNF inhibitors by performing a pooled-analysis of randomized clinical trials that evaluated efficacy of TNF inhibitors compared to placebo in subgroups of interest.

Methods

1. *Systematic literature review*

A systematic review of randomized controlled clinical trials was performed according to PRISMA guidelines (39), with the aim of studying the efficacy of TNF inhibitors according to different demographic and disease-related factors. The protocol (**Supplemental document 1**)

was registered in the PROSPERO database (number CRD42018071079) in January 2018. In January 2017, we searched for randomized controlled trials (RCT) and meta-analyses of RCT in Cochrane Central Register of Controlled Trials (CENTRAL). This research was performed, using as keywords "rheumatoid arthritis" and the names of the different TNF inhibitors. Two authors (TBA and SD) selected eligible RCT according to title and abstract. Full texts of the eligible articles were retrieved in order to decide for their final inclusion (SD and TBA). The studies were included if they were RCT comparing one or more TNF inhibitors to placebo or conventional therapy, and included patients with RA. We then searched for RCT that reported the efficacy of TNF inhibitors according to one or more disease activity scores by subgroups of interest. We considered the following factors: smoking status, physical activity, gender, age, BMI, ACPA and RF status, RA disease duration, DAS28(CRP) baseline level. Non-randomized clinical trials, observational studies, RCT comparing two TNF inhibitors without a placebo control group or csDMARD were excluded.

2. Data collection

Given the unavailability of subgroup of interest analyses, we contacted the corresponding authors and/or sponsors of these studies in order to obtain aggredated data and/or individual patient data (IPD) and perform the pooled analysis. Since most of the data were stored securely on data sharing platforms, we requested each of these platforms an access to the raw dataset.

3. Data management

After obtaining access to data, either directly from the data curator (for three trials) or via a datasharing plateform remotely, we first analysed the efficacy of TNF inhibitors compared to control in subgroups of interest. These subgroups were: smoking status (never / ever smokers), current physical activity (yes / no), gender (men / women), age (≤ 50 / >50 years), BMI (<30 / ≥ 30 kg/m^2 defining obesity), RF status (positive / negative), ACPA status (positive / negative), RA disease duration defined as the time from the diagnosis (< 2 / 2 to 10 / ≥ 10 years), baseline DAS28(CRP) (≤5.1 / > 5.1).

4. Outcomes

The predefined primary end-point was ACR20 score after 6 months of follow up, and secondary end-points were ACR50, ACR70, DAS28(CRP) and DAS28(ESR). The primary endpoint was changed post hoc to between-group difference in DAS28(CRP) change from baseline to 6 months (or 3 months if only available) (ΔDAS28(CRP)). Secondary endpoints were therefore

changed post hoc to between-group difference in DAS28(CRP) at 6 months (or 3 months if only available) and EULAR response criteria at 6 months (or 3 months if only available) (40) : patients are classified as good responders if they have a final DAS28 less than or equal to 3.2 and a DAS28 improvement from baseline at least 1.2, none-responders are those with a final DAS28 over 5.1 and a DAS28 improvement from baseline less than or equal to 1.2 ; patients with a DAS28 improvement from baseline of 0.6 or less are also classified as non-responders ; the moderate responders are those who do not meet these previous criteria. Post hoc changes were made due to the absence of erythrocyte sedimentation rate (ESR) and Health Assessment Questionnaire (HAQ) in most studies necessary to calculate ACR. Exploratory outcomes included tender joint count 28 (TJC28), swollen joint count (SJC28), patient global assessment (PGA) and C-reactive protein (CRP). Between-group differences in baseline to 3 or 6 months changes outcomes (ΔTJC28, ΔSJC28, ΔPGA and ΔCRP) and between-group differences in 3 or 6 months outcomes (TJC28, SJC28, PGA and CRP) were estimated.

5. Statistical analyses

Statistical analyses were performed using R Studio software. Descriptive results are presented as median (min-max) or mean (interquartile range) unless stated otherwise.

a. Meta-analysis on pooled data

Pooled odds ratios (OR) and mean difference (MD) with 95% Confidence intervals (95% CI) for EULAR responders and for DAS28(CRP) differences respectively, between TNF inhibitors and placebo, were calculated using two step meta-analyses. First, aggregate data regarding treatment response in each subgroup of interest was estimated from IPD. Second, a random-effect Mantel-Haenszel model was applied to calculate pooled effect. Between-study heterogeneity was quantified using Cochrane Q and I^2 statistics. Heterogeneity was considered low if I^2 <=30%, moderate if I^2 30 to 50%, substantial if I^2 50% to 70% and considerable if I^2 >=70%.

b. Meta-regression analysis on individual data

Individual patients data were accessed from YODA and VIVLI data sharing platforms. The data from these platforms were used separately to perform linear meta-regressions of the 3 or 6 month DAS28(CRP), adjusted on baseline DAS28(CRP), trial, and treatment by covariate interaction (bivariate analyses). Multivariate metaregression of the 6 month DAS28(CRP),

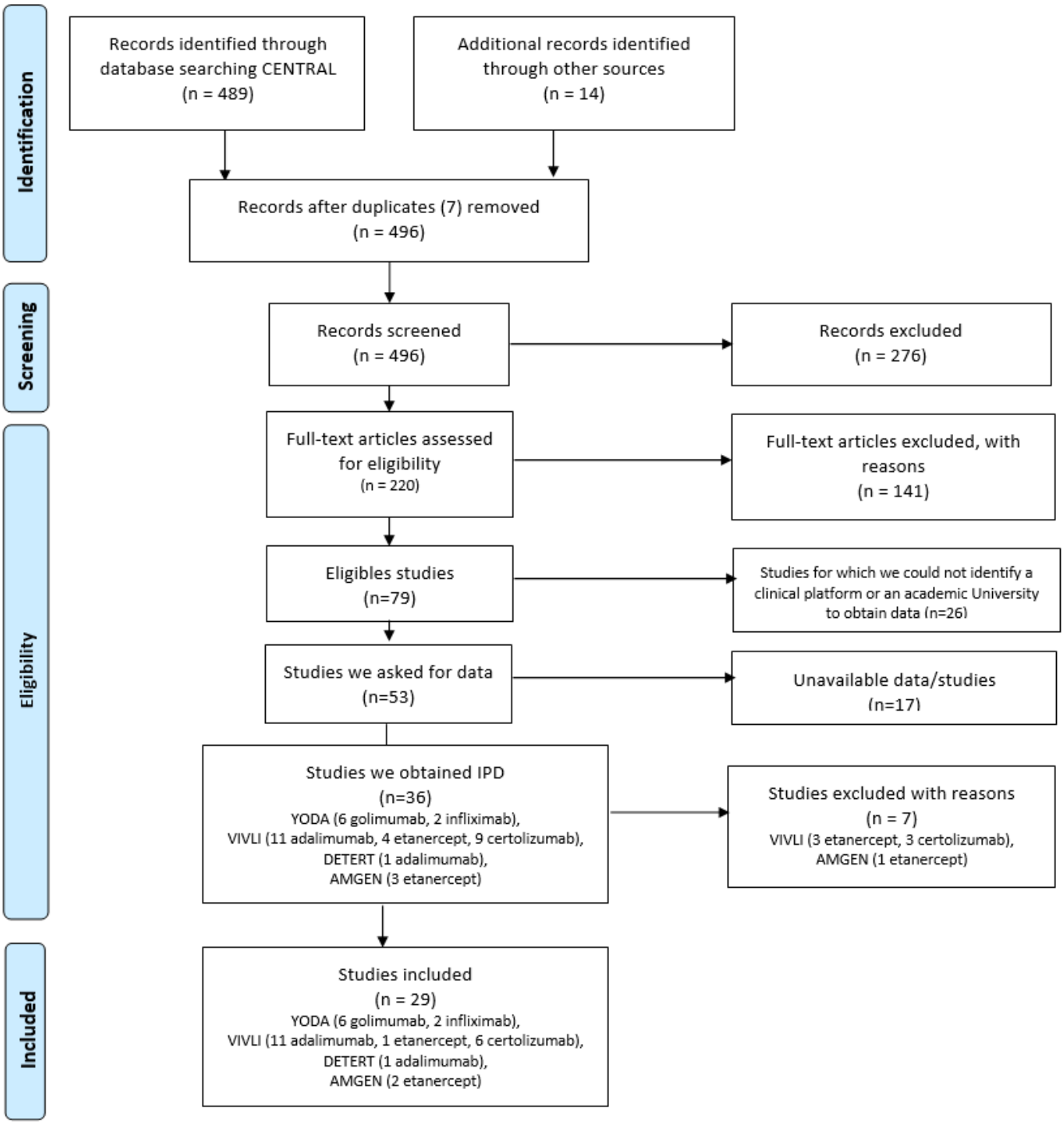
adjusted on baseline DAS28(CRP), trial, age and all other covariates with a significant effect in bivariate analyses were also performed.

Results

Search process

We found 496 articles published between 1994 and 2017, of them 220 were eligible after selection on title and abstract, and 79 fulfilled all inclusion and exclusion criteria. At the end of our search, we did not retrieve any RCT that reported results regarding the efficacy of TNF inhibitors in the subgroups of interest. We therefore contacted the authors, sponsors, platforms and universities of these 79 articles in order to retrieve IPD to produced our own aggregated data. Some studies were further excluded due to inconsistency with our protocol (**Supplemental document 2**). As to June 2021, we obtained access to data for 29 studies (**Figure 4**).

Figure 4: Flow diagram of studies selection process.



Characteristics of included studies and analyzed patients

This pooled analysis included 29 studies evaluating five TNF inhibitors: 12 evaluated adalimumab, 3 evaluated etanercept, 6 evaluated certolizumab, 6 evaluated golimumab and 2 evaluated infliximab (**Supplemental document 3**). All of them were double blind, placebo controlled, parallel group studies, conducted between 1997 and 2015. The median number of patients randomized was 444 (range: 47 to 1648).

Overall, individual data of 14,838 randomized patients were available. (**Table 1)**. Clinical and biological data was missing in some studies, leading to 11,617 (78%) analyzed patients. Physical activity's data was missing for 25 studies included in this analysis. Some data could not be retrieved for confidentiality and anonymisation reasons, such as patients age in 6 certolizumab studies and disease duration in 4 certolizumab studies that were reported as intervals. Treatment response could be evaluated at week 30 for 2 studies, at week 24 for 21 studies, at week 26 for 2 studies and at week 12 for 4 of them.

Table 1 Baseline characteristics of analyzed subjects

STUDIES	Analyzed patients (%)	Smoker (%)	Physical activity (%)	Women (%)	Mean Age (yrs)	Mean BMI (kg/m2)	RF positive (%)	Anti CCP positive (%)	Mean Duration (yrs)	TJC28 (sd)	SJC28 (sd)	PGA (sd)	CRP (mg/l) (sd)	DAS28(CRP) (sd)
NCT00647491	312 (89)			79.5	54.5	21.9	90.4		9.4	15(6)	13.7(5.3)	70.3(20.7)	57.9(36.4)	6.5(0.8)
NCT00420927	857 (83)	49.8		74.7	49.7	28	88.7	84.5	0.3	15.7(6.6)	12.4(5.8)	63.2(22.7)	28.8(31.7)	6(1)
NCT00195663	630 (79)			74.8	52.1	27.1	84		0.8	16.8(6.2)	14.3(5.6)	65.4(23.5)	38.7(39.1)	6.3(0.9)
NCT00195702	492 (79)			74.4	56	28.6	85.5		10.9	14.6(6.5)	13.2(5.5)	52.9(22)	18.1(18.4)	5.7(0.8)
NCT00234845	94 (63)	48.9		58.5	47.6	26.9	64.5	57	0.7	13.3(7.3)	10.3(5.8)	61(25.4)	30.1(34.6)	5.6(1.2)
NCT00235859	118 (92)	13.6		89.8	48.5	22.4	75.4			10.9(4.5)	8.7(4)	60.5(19)	24.2(23.2)	5.4(0.8)
NCT00647920	43 (91)	20.9		79.1	52.5	24	94.9		7.2	13.8(6.4)	12.8(4.4)	71.8(14.1)	22(24.9)	5.9(0.8)
NCT00538902	278 (92)	13.3		83.5	48.8	22.7	83.1		7	13.8(8)	8.7(5.6)	60.4(19.8)	21(24.5)	5.5(1.1)
NCT00647270	336 (80)	57.1		76.8	56	28.7	66.4		6.9	16.7(7.1)	13.4(6.1)	54.2(22.6)	13.9(18.3)	5.7(0.9)
DE31	574 (90)			80.1	55.3	28	75.7		10.3	14.8(6.6)	13.8(5.8)	52.8(22.5)	14.8(17.8)	5.7(0.9)
NCT00870467	264 (79)	36		80.7	54.6	22.4	83.3	83	0.3	13.1(5.9)	11.6(4.9)	62.4(24.3)	24.8(25.8)	5.7(1)
PMID22739990	134 (78)			70.1	49.8		69.5	53.4						
PMID9920948	64 (72)			92.2		26.2	93.7		13.1	14(7.6)	13.5(6.2)	55.6(17.7)	25.8(25.3)	5.8(1)
NCT01313208	195 (93)			75.9		30			7.7				9(14.8)	
NCT00445770	462 (84)			80.7	51.2	22.1	77.5			9.7(5.6)	8.7(4.8)	56.2(22.8)	19.9(21.9)	5.2(1)
NCT00160602	368 (62)				*	26.2	78.1	*		17.9(6.4)	14.5(5.4)	61.8(20)	24.5(26.1)	6.2(0.8)
NCT00152386	587 (62)			84.2	*	27	84.5	*		17.5(6.2)	14.8(5.4)	63.7(19.3)	25(28.4)	6.2(0.8)
NCT00717236	936 (57)				*	30.1	74.9	67.2		14.6(6.5)	11.6(5.4)	59.3(21.7)	17(21)	5.7(0.9)
NCT00548834	103 (47)			78.6	*	27.3	71.6	*	8.6	16.1(6.5)	13.6(5.7)	32.3(8.2)	18.4(21.9)	5.5(0.9)
NCT00674362	143 (74)			82.5	*	26.7	75.9	*		3.9(1.6)	3.4(1.5)	35.3(17.3)	12.2(15.1)	3.8(0.4)
NCT01519791	860 (98)	46.3		76.9	*	27.9	96	84.3	0.2	15.7(6.5)	12.5(5.5)	65.2(22)	21.4(28.8)	5.9(1)
NCT00264537	566 (89)	32.3	13.6	84.6	49	27.1	82.5	73.7	2.5	14.5(7.3)	10.7(6)	60.5(23.3)	24.9(31.1)	5.7(1.1)
NCT00264550	396 (89)	38.9	18.9	82.1	49.9	27	83.7	80	5.9	13.5(7.3)	9.6(5.5)	55.3(24.2)	17.9(23.2)	5.4(1)
NCT00299546	335 (73)	51	25.1	78.8	53.1	28.4	73.4	72.7	8.5	15.5(7.3)	11.4(5.9)	63.7(22.2)	17.2(24.7)	5.7(1)
NCT00361335	567 (88)	34.9	23.5	82	49.2	26.8	84.7	79.1	5.9	14(7)	10.5(5.3)	60.1(21.5)	17.5(21.6)	5.6(1)
NCT00973479	546 (92)			81.5	51.6	26.9	91.7	92.4	4.4	10.4(4.2)	7.5(3.4)	64.9(18.4)	27.2(26.5)	5.4(0.8)
NCT01248780	234 (89)	9.4	28.2	80.8	46.9	22.6	100	93.1	1.7	8.8(4.8)	5.8(3.7)	62.5(21.6)	19.1(22.4)	4.9(1)
NCT00269867	276 (64			78.6	50.8	27.5	79	35.6	5.3	15.8(7.5)	14.6(6.4)	59.4(22.4)	36.9(38.8)	6.1(1)
NCT00236028	847 (81)			71.2	49.7	27.9	71.8		0.8	17.5(6.6)	14.4(5.3)	61.6(24.5)	27.8(32.9)	6.2(0.9)

* Exacts Data replaced by specifics intervals. Blue denotes adalimumab, pink etanercept, orange certolizumab, yellow golimumab and red infliximab.

Difference in ΔDAS28(CRP) between baseline and 3 or 6 months

Smoking status, physical activity, gender, age, BMI, ACPA, RF status, disease duration, and baseline DAS28(CRP) did not significantly influence the difference in ΔDAS28(CRP) between TNF inhibitors and placebo in subgroup analyses (p>0.05 for subgroup differences, **Table 2 and Table 3**). We observed a trend for the TNF inhibitors to be more effective in patients aged <=50 (MD -0.70, 95% CI [-0.83 ; -0.57]) compared to patients >50 (MD -0.54, 95% CI [-0.67 ; -0.41]), p=0.08 for subgroups difference. Heterogeneity was considerable (I^2 >=70%) in some subgroups: non-smoking patients, women, non-obese patients, patients with RF and ACPA positive status, and patients with high baseline DAS28(CRP).

Difference in final DAS28(CRP)

Smoking status, physical activity, gender, age, BMI, ACPA and RF status, disease duration, and baseline DAS28(CRP) did not significantly influence the final DAS28(CRP) between TNF inhibitors and placebo in subgroup meta-analyses (p>0.05 for subgroup differences, **Supplemental document 4**). We observed a trend for the TNF inhibitors to be more effective in patients with a longer disease duration (MD -0.78 [-1.05 ; -0.50]) compared to patients with a shorter disease duration of less than 2 years (MD -0.52 [-0.70 ; -0.34]), p=0.07 for subgroups difference (**Table 3**). Heterogeneity was considerable (I^2 >=70%) in some subgroups: women, non-obese patients, patients with positive RF and ACPA status, and patients with high baseline DAS28(CRP).

Good EULAR response

Smoking status, physical activity, gender, age, BMI, ACPA or RF status, disease duration, and baseline DAS28 did not significantly influence the good EULAR response between TNF inhibitors and placebo in subgroup meta-analyses (p>0.05, **Supplemental document 5**). Substantial heterogeneity was observed for some subgroups: non smokers, RF positive and a baseline DAS28 >5.1.

EULAR Non-response

We observed a qualitative and significant influence of obesity on the odd of being EULAR non-responder between TNF inhibitors and placebo (**Supplemental document 6**). Obese patients had a higher risk of non response (OR 0.52 [0.43 ; 0.63]) compared to patients with a BMI<30 (OR 0.36 [0.30 ; 0.45]), p=0.01 for subgroup difference (**Table 3**). There was no influence of

other covariates (smoking status, physical activity, gender, age, baseline DAS28(CRP), disease duration, ACPA and RF status) on the odd of non-response between TNF inhibitors and placebo (p>0.05 for subgroups differences). There was a trend for negative RF status to be associated with a higher risk of non-response (0.48 [0.38 ; 0.61]) compared to positive RF status (0.38 [0.31 ; 0.46]), p=0.13 for subgroup difference. Substantial heterogeneity was observed for some subgroups: non smokers, women, BMI<30, positive RF and ACPA status, and baseline DAS28>5.1.

Exploratory outcomes: reductions in final TJC28, SJC28, PGA, and CRP

Disease duration influenced the mean final TJC28 and SJC28 counts between TNF inhibitors and placebo with higher final reductions in patients with a disease duration >=10 years compared to patients with a disease duration < 2 years, p<0.01 and 0.07 for subgroup differences respectively (**Supplemental document 7**).

Baseline DAS28(CRP) influenced the mean final TJC28, SJC28 and CRP between TNF inhibitors and placebo with higher final reductions in patients with baseline DAS28(CRP) >5.1 compared to patients with baseline DAS28(CRP) <=5.1, p=0.07, <0.01 and 0.04 respectively (**Supplemental document 7**). Patients with a RF positive status had higher CRP reductions than patients with negative RF status, p<0.01 for subgroup differences.

Exploratory outcomes: differences in ΔTJC28, ΔSJC28, ΔPGA, ΔCRP between TNF inhibitors and placebo

We observed the same pattern of results as described for final TJC28, final SJC28, final PGA, final CRP between TNF inhibitors and placebo with less significant results (**Supplemental document 8**).

Table 2: Mean difference in ΔDAS28(CRP) between baseline and 3 or 6 months by clinical and biological baseline characteristics.

	Number of studies	Number of patients		Mean Difference (95% CI)	Heterogeneity		p for subgroup difference
		TNF inhibitors	Placebo		I^2 (%)	*p*	
Smoking							
Yes	14	1409	685	-0.50 [-0.67 ; -0.32]	36	0.09	0.87
No		2329	1070	-0.47 [-0.65 ; -0.29]	70	0.01	
Physical activity							
Yes	5	297	138	-0.38 [-0.65 ; -0.11]	0	0.79	0.81
No		1191	472	-0.42 [-0.66 ; -0.18]	67	0.02	
Gender							
Women	27	5585	2513	-0.62 [-0.75 ; -0.49]	76	0.01	0.34
Men		1526	689	-0.52 [-0.68 ; -0.36]	27	0.11	
Age							
>50	27	4760	1876	-0.54 [-0.67 ; -0.41]	64	0.01	**0.08**
<=50		3315	1407	-0.70 [-0.83 ; -0.57]	51	0.01	
BMI							
>= 30	28	2125	828	-0.55 [-0.66 ; -0.44]	0	0.70	0.20
< 30		5977	2492	-0.66 [-0.80 ; -0.52]	78	< 0.01	
RF status							
Positive	28	6480	2668	-0.65 [-0.78 ; -0.52]	75	< 0.01	0.12
Negative		1425	559	-0.50 [-0.64 ; -0.37]	5	0.39	
ACPA status							
Positive	13	3058	1462	-0.50 [-0.71 ; -0.29]	82	< 0.01	0.62
Negative		920	368	-0.43 [-0.62 ; -0.24]	14	0.31	
Disease duration							
< 2 years	22	2781	1416	-0.53 [-0.72 ; -0.34]	66	< 0.01	0.25
2-10 years		1104	535	-0.51 [-0.68 ; -0.35]	27	0.14	
=>10 years		688	333	-0.77 [-1.03 ; -0.50]	47	0.03	
Baseline DAS28							
> 5,1	27	6097	2344	-0.63 [-0.77 ; -0.50]	74	< 0.01	0.27
<= 5,1		1948	899	-0.53 [-0.66 ; -0.39]	52	< 0.01	

ACPA = Anti-citrullinated protein antibodies, Baseline DAS28 = DAS28(CRP) score at baseline, BMI = Body Mass Index, RF= Rheumatoid factors.

Table 3: p values for subgroup difference for ΔDAS28(CRP), DAS28(CRP) final, good EULAR response and non-EULAR response between TNF inhibitors and placebo

	Number of studies	p-value for subgroup difference			
		ΔDAS28(CRP)	DAS28(CRP) final	Good EULAR response	EULAR Non-response
Smoking					
Yes	14	0.87	0.77	0.95	0.97
No					
Physical activity					
Yes	5	0.81	0.58	0.87	0.95
No					
Gender					
Women	27	0.34	0.64	0.50	0.94
Men					
Age					
>50	27	**0.08**	0.15	0.59	0.34
<=50					
BMI					
>= 30	28	0.20	0.12	0.22	**0.01**
< 30					
RF status					
Positive	28	0.12	0.28	0.61	0.13
Negative					
ACPA status					
Positive	13	0.62	0.99	0.79	0.29
Negative					
Disease duration					
< 2 years	22	0.25	**0.07**	0.69	0.33
2-10 years					
=>10 years					
Baseline DAS28					
> 5.1	27	0.27	0.44	0.73	0.31
<= 5.1					

ACPA = Anti-citrullinated protein antibodies, Baseline DAS28 = DAS28(CRP) score at baseline, BMI = Body Mass Index, RF= Rheumatoid factors.

Metaregression analyses

Bivariate and multivariate metaregressions results are shown in **Table 4**. Metaregressions were performed on 7,457 patients (18 RCT) from the Vivli datasharing plateform and on 3,767 (8 RCT) patients from the YODA platform.

Bivariate analyses indicated that being treated by TNF inhibitors was associated with a significantly lower 6 months DAS28(CRP) while a higher baseline DAS28(CRP) was associated with a significantly higher 6 months DAS28(CRP) in trials from both databases. Male gender was correlated with a lower 6 months DAS28(CRP) and a longer disease duration were associated with a higher 6 months DAS28(CRP) in trials from Vivli database. Significant treatment effect modifiers in bivariate analyses were disease duration with a lower 0.02/year (in trials from Vivli database) and baseline DAS28(CRP) with a higher 0.1/baseline unit (in trials from YODA database) 6 months DAS28(CRP) in treated patients.

Four variables, i.e. age, gender, BMI and disease duration, were included in the multivariate models. Using the individual data from Vivli (n= 7,457), the model indicated that disease duration as a continuous variable and baseline DAS28(CRP) as a categorial variable significantly modified treatment effect on 6 months DAS28(CRP). Patients treated by TNF inhibitors had a final DAS28(CRP) decreased by 0.02 for each year of disease duration ($p<0.001$), and a 0.21 decreased for patients with a baseline DAS28(CRP)>=5.1 ($p=0.05$). These results were not observed in the metagression performed on the 3,767 patients from the YODA platform.

Table 4: Bivariate and multivariate metaregression analyses for the 3 or 6 months DAS28(CRP)

	Yoda platform (3,767 patients)			**Vivli platform (7,457 patients)**		
	Standardized Coefficient	SD	p-value	Standardized Coefficient	SD	p-value
Bivariate						
Smoking	0.051	0.09	0.58	0.09	0.08	0.27
Exercise	-0.23	0.12	**0.06**			
Men	-0.15	0.09	0.12	**-0.26**	**0.07**	**<0.001**
Age*	0.003	0.003	0.28	-0.003	0.002	0.17
BMI*	0.002	0.006	0.75	**0.015**	**0.004**	**<0.001**
RF +	-0.15	0.10	0.15	0.40	1.22	0.74
ACPA +	-0.18	0.11	0.11	0.27	0.29	0.36
Duration*	0.005	0.01	0.70	**0.013**	**0.005**	**<0.001**
Baseline DAS28 (CRP)	**0.54**	**0.04**	**<0.001**	**0.56**	**0.03**	**<0.001**
Treatment	**-0.47**	**0.04**	**<0.001**	**-0.63**	**0.03**	**<0.001**
Treatment by covariate interaction						
Treatment: Smoking	-0.003	0.11	0.97	0.02	0.10	0.81
Treatment: Exercise	0.054	0.14	0.71			
Treatment: Men	-0.11	0.11	0.32	0.14	0.08	**0.08**
Treatment: Age	-0.0005	0.004	0.89	0.006	0.003	**0.06**
Treatment: BMI	0.006	0.0077	0.43	0.002	0.005	0.63
Treatment: RF+	0.02	0.12	0.86	0.85	1.34	0.53
Treatment: ACPA+	0.12	0.13	0.33	0.04	0.32	0.89
Treatment: Duration	0.01	0.015	0.41	**-0.02**	**0.005**	**<0.001**
Treatment: Baseline DAS28(CRP)	**0.1**	**0.04**	**0.03**	-0.04	0.03	0.22
Multivariate**						
Treatment: Duration	0.02	0.02	0.32	**-0.02**	**0.006**	**<0.001**
Treatment: Baseline DAS28(CRP)	0.08	0.01	0.44	-0.02	0.04	0.7
Treatment: Baseline DAS28(CRP)>5.1	0.33	0.23	0.15	**-0.21**	**0.11**	**0.05**

* for one unit (year, kg/m^2)

** Gender, age, BMI, disease duration

Discussion

From the meta-analysis on pooled data the sole caracteristic associated with a clinical outcome was body mass index, which increased the odd of being non responders. According to the metaregression analysis based on individual data, the final model found that disease duration and baseline DAS28(CRP) categories interacted with the final DAS28(CRP). In the present work, we did not find any influence of smoking status, physical activity, gender, age, RF or ACPA status on response to TNF inhibitors, which was in accordance to previous meta-analyses **(25)** and registries **(21)** but not with other retrospective cohorts **(22) (25)**.

A recent study based on IPD from five RCT showed that an increase in BMI was associated with a lower frequency of remission when using SDAI ($p = 0.001$) and CDAI ($p = 0.001$) among patients treated by csDMARD or bDMARD, or TCZ **(41)**. It is known that volume of distribution of TNF inhibitors is increased with body size. This explain a decreased TNF inhibitor concentration and thus may account for the lesser clinical response **(42)** as compared with non-obese patients **(43)**. The effect of body mass index was only seen when considering the odd of being non responders according to EULAR criteria, though. This highlights the differences in assessing the clinical outcomes using EULAR criteria, criteria for remission, CDAI criteria, SDAI criteria or ACR criteria. Still, bodyweight has a significant impact on response and rheumatologists should control bodyweight in RA while starting a TNF inhibitor.

We observed that patients with long disease duration, i.e. ≥10 years, seemed to have a better response than others, which was not reported in the literature so far. In clinical practice, patients with long disease duration who require TNF inhibitors are usual those who have already failled to various treatments, which is known as a poor prognostic factor **(16)**. This surprising result was seen in one of the datasharing platform and was not attributed to age nor disease activity. Thus, patients with long standing disease with insufficent control of disease activity are as eligible as those with shorter disease duration, with even an additional effect of TNF inhibitors.

High baseline disease activity, e.i. DAS28(CRP)>5.1, was predictive of a favorable, although small, additional reduction in DAS28(CRP) at the time of 3 and 6 months, as compared with patients with moderate disease activity. It seems coherent that patients with the highest inflammatory burden obtain a tangible effect as compared with those with less inflammation, in which the disease improvement is less pronounced. This finding was only observed by the metaregression analysis issued from one datasharing platform. The metaanalysis of pooled data yielded no statistically significant difference but pointed to the same direction.

Our results regarding tobacco disagree with those from the EIRA cohort, and those from the English, Portuguese and Swedish registers, which showed an association between active smoking and a poorer response to TNF inhibitors at 3 and/or 6 months and a lower rate of remission **(11) (12) (14)**. Mattey *et al.* found that RA patients with a history of smoking were more likely to have a poorer response to TNF inhibitors than non-smokers. The treatment failure due to smoking was associated with the intensity of previous smoking, irrespectively of smoking status at treatment initiation **(44)**. In a study from the Swedish Rheumatology Register cohorts, current smokers were less likely to achieve a good EULAR response at 3 months after starting a TNF inhibitors than in non-smokers (29% versus 43%; p=0.03; 535 patients) **(13)**. In our study, we splitted the population into ever (past or active) smokers versus never smokers because the information of former past or active smoker was not available for some studies, as well as the duration of smoking or quantity of cigarettes smoked, which may have decreased the possibility of showing an effect of tobacco on clinical response.

Our study has some strengths that deserve to be mentioned. This is the first analysis based on a large amount of IPD, studying the effect of demographic and disease factors on response to TNF inhibitors in RA which allowed us to increase the power to show a very small difference between some subgroups of patients. The current knowledge are predominantly based on national registries, retrospective cohorts, or agregate data meta-analyses. The use of IPD from data-sharing platforms enables reusing raw data from a substantial number of studies. Furthermore, in comparison with meta-analyses based on aggregated data published by the investigators, obtaining raw data allowed us to study in a standardised manner various parameters and to pool them together creating a large database. The results obtained here have important clinical impacts in the context of personalized treatment strategy, for example to increase awareness on negative predictive factors such as obesity when initiating a TNF inhibitor.

Nevertheless, this study has limitations that are important to point out. The main limitation of this study was the missing data. In most cases, we chose to exclude from the subgroup analysis patients who could not be categorised, which may have caused bias in the analysis **(45)**. Some adjustments were nevertheless made to limit this loss of data. For instance we adapted the age intervals provided by the sponsor to our population sub-groups, seeking for the best compromise (**Supplemental document 9**). Similarly, the absence of ESR in some studies led us to use DAS28(CRP) and ΔDAS28(CRP) in the categorisation of responder and non-responder patients instead of DAS28(ESR) and ΔDAS28(ESR). In a large Japanese cohort of

3,073 rheumatoid arthritis patients, it was shown that the use of CRP in DAS28 overestimated the EULAR response compared to DAS28 using ESR **(46)**, due to different cut-off points for categorising rheumatoid arthritis activity between CRP and ESR **(47) (48)**. One study found that very high disease activity defined by a DAS28(ESR) of 5.1 was correlated with a DAS28(CRP) score of 4.6. The management of missing data may have differed from published articles on some studies and led to different results. This was the case for the NCT00870467 study evaluating adalimumab, in which the authors used a Last Observation Carried Forward method (LOCF) by using the last observed non-missing value to fill in missing values at a later point in the study **(49)**. Thus, our analysis showed a greater reduction in DAS28(CRP) in the placebo group versus TNF inhibitors group in this methotrexate naive population (**supplemental document 10, 11, 12, 13, 14**). We performed a sensitivity analysis excluding this study from the pooled analysis and found similar results, except for a greater significance of the p-values for the BMI subgroups (**supplemental document 15**).

Another limitation of our study is the different time point of response assessment, i.e. at week 30 for 2 studies, at week 24 for 21 studies, at week 26 for 2 studies and at week 12 for 4 of them (**supplemental document 10, 11**). We made a compromise in order to include as many patients as possible in the analysis and to stick to the clinical relevance. In the treat-to-target strategy **(9)**, European recommendations allow and require the clinician to evaluate the response treatment as early as 3 months.

For all the studies, we cathegorized treatment arms into two groups, either placebo or TNF inhibitors, whereas there were often several different TNF inhibitors groups with different dosages. Almost all studies have investigated the efficacy of the combination of TNF inhibitors and methotrexate to placebo. This makes it difficult to interpret how much variability in response is associated with TNF inhibitors or methotrexate. It has in fact already been shown that there is a difference in response to methotrexate in rheumatoid arthritis in some subgroups : men respond better to methotrexate treatment than women **(50) (51)**.

Another possible criticism of our study might be our choices of criteria's cutoff such as age (≤50 versus >50), BMI (<30 versus ≥30) or disease duration (<2 years – between 2 and 10 years - ≥ 10 years), baseline DAS28(CRP) (≤5,1 versus 5,1). We tried to have relevant cutoffs both from the clinical point of view, and to have sufficient patient numbers for the statistical analysis.

Finally, we observed persistent heterogenicity among studies, on the response outcomes. This might be explained by a methodological heterogenicity in the studies such as differences

on inclusion criteria or different study design but also by a difference in response between the five TNF inhibitors, which might be worth studying the response of each TNF inhibitors in the subgroups of interest. It was not possible to pool the individual data from the differences sources (YODA, Vivli, AMGEN and DE31) altogether. This would have strengthen our conclusion, but there is no possibility to extract the eletronic files from the platforms.

Conclusion

In our study, the response of TNF inhibitors in rheumatoid arthritis does not appear to vary according to smoking status, physical activity, age, gender, autoantibody profile. A significantly higher EULAR non-response rate was observed in obese patients which emphasises the need to control bodyweight in RA while starting a TNF inhibitor. Longer disease duration and high disease activity at baseline seems to be associated with an increase in response's magnitude.

Declaration

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: The raw data were not extracted but analyzed remotely from the YODA and Vivli platforms.

Competing interests: The authors declare that they have no competing interest.

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Authors' contributions: SD initiated the project, wrote the protocol of the meta-analysis, selected the studies and asked for data, M-A S and JLW ensured to obtain data, analyzed the results and drafted the manuscript; NA handled the database and help improving the manuscript; TBA performed the statistical analyses and help draft the manuscript; DM: coordinated the work, participated in the interpretation of the analyses and help draft the manuscript. PG contributed to the interpretation of the results and manuscript improvement; JD provided IPD from a study evaluating adalimumab. All authors read and approve the final version of the manuscript.

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Annexes

Supplemental document 1 : Protocole PROSPERO

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PROSPERO
International prospective register of systematic reviews

Influence of demographic and environmental factors on anti-TNF efficacy in rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials

Sophie Derolez, Theodora Bejan-Angoulvant, Denis Mulleman

Citation

Sophie Derolez, Theodora Bejan-Angoulvant, Denis Mulleman. Influence of demographic and environmental factors on anti-TNF efficacy in rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. PROSPERO 2018 CRD42018071079 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018071079

Review question

Patients: Adults (?18 years of age) with RA according to ACR 1987 or ACR/EULAR 2010 criteria.

Interventions: all anti-TNF drugs (infliximab, adalimumab, etanercept, golimumab, certolizumab), either alone or in combination with conventional DMARD.

Comparator: placebo or conventional DMARD, including corticosteroids, methotrexate, salazopyrine or leflunomide.

Outcomes:

- primary: ACR20

- secondary: ACR50, ACR70, DAS28-CRP, DAS28-ESR, CDAI, SDAI

Searches

Search strategy:
For the first step, we searched CENTRAL and selected eligible studies. After review of full-text articles, we observed that data of interest were very rarely reported. We therefore decided to ask the data from the authors. We will complete the search in two other electronic databases: PubMed and EMBASE, and perform hand searches of references list of included studies or relevant reviews and meta-analyses. We will also search clinical trial registries in search of unpublished clinical trials.
Selection of articles
We will select potential articles on title and abstract, then assess the full eligibility criteria on the full-text articles.
Data collection and analysis
Study selection
- First step: eligible studies selected by title and abstract: randomized controlled trial evaluating the efficacy of an anti-TNF compared to placebo or DMARD in RA.
- Second step: review of the full text of eligible studies and inclusion of studies that reported data of efficacy by subgroups of interest. At this step, reasons for exclusion will be registered.
We will extract the following data: age, sex, BMI, physical activity, smoking status, disease duration, DAS28, CRP, ACPA status, RF status, author, year of publication, study acronym, journal, PMID, NCT or clinical trial registry number, anti-TNF evaluated and type of control, number of patients included, main outcome, time for main outcome, duration, extension, sponsor.
Assessment of risk of bias following the Cochrane Risk of Bias Tool for randomized controlled trials will be evaluated in duplicate.

Types of study to be included

Randomized controlled trials.

Condition or domain being studied

Clinical trials being the less prone to bias, we decided to consider the randomized controlled trials which

reported the effect of factors that modify treatment effects (interaction factors).
- Inclusion criteria: randomized controlled trials comparing an anti-TNF drug (infliximab, adalimumab, golimumab, certolizumab pegol or etanercept) versus placebo or conventional DMARDs, in rheumatoid arthritis (RA) patients and reported efficacy data by subgroups of demographic and disease related factors of interest.
The following factors of interest will be considered: age, sex, BMI, smoking status, disease duration, DAS28, CRP, ACPA, RF, and physical activity.
- Exclusion criteria: non-randomized controlled trials, observational studies, randomized trials comparing 2 anti-TNF drugs without a control group.

Participants/population
Adults (?18 years of age) with Rheumatoid Arthritis (RA) according to ACR 1987 or ACR/EULAR 2010 criteria.

Intervention(s), exposure(s)
Interventions: all anti-TNF drugs (infliximab, adalimumab, etanercept, golimumab, certolizumab), either alone or in combination with conventional DMARD.

Comparator(s)/control
Comparator: placebo or conventional DMARD, including corticosteroids, methotrexate, salazopyrine or leflunomide.

Main outcome(s)
ACR20.

Additional outcome(s)
ACR50, ACR70, DAS28-CRP, DAS28-ESR, CDAI, SDAI.

Data extraction (selection and coding)
- First step : eligible studies selected by title and abstract: randomized controlled trial evaluating the efficacy of an anti-TNF compared to placebo or DMARD in RA.

- Second step : review of the full text of eligible studies and inclusion of studies that reported data of efficacy by subgroups of interest. At this step, reasons for exclusion will be registered.

We will extract the following data: age, sex, BMI, physical activity, smoking status, disease duration, DAS28, CRP, ACPA status, RF status, author, year of publication, study acronym, journal, PMID, NCT or clinical trial registry number, anti-TNF evaluated and type of control, number of patients included, main outcome, time for main outcome, duration, extension, sponsor.

Risk of bias (quality) assessment
Assessment of risk of bias following the Cochrane Risk of Bias Tool for randomized controlled trials will be evaluated in duplicate.

Strategy for data synthesis
Statistical analysis:

A meta-analysis of aggregate data will be performed, following appropriate methods (relative risks or standardized mean difference) depending of the nature of the outcome considered. A fixed effect model will be performed first, with addition of a random effect model in case of significant heterogeneity. Heterogeneity will be considered significant if the m-value of the heterogeneity test is <0.10 or I^2 is higher than 50%.

Analysis of subgroups or subsets
Subgroups analyses of efficacy by age, sex, BMI, smoking status, disease duration, DAS28, CRP, ACPA, RF, and physical activity.

Intervention : all anti-TNF drugs (infliximab, adalimumab, etanercept, golimumab, certolizumab), either alone or in combination with conventional DMARD.

Randomized controlled trials.

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Type and method of review
Epidemiologic, Meta-analysis, Systematic review

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None known

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English

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Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Antirheumatic Agents; Arthritis, Rheumatoid; Demography; Humans; Tumor Necrosis Factor-alpha

Date of registration in PROSPERO
29 January 2018

Date of first submission
20 January 2018

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

29 January 2018

Supplemental document 2: Overview of data requested, obtained, analyzed with reason for non-inclusion for ADA, ETN, and CZP

TNF inhibitors	Sponsor	Data requested	Data obtained	Data analysed	Reasons
Adalimumab	Abbvie	NCT00647491	Yes	Yes	
	Abbvie	NCT00420927	Yes	Yes	
	Abbvie	NCT00195663	Yes	Yes	
	Abbvie	NCT00195702	Yes	Yes	
	Abbvie	NCT00234845	Yes	Yes	
	Abbvie	NCT00235859	Yes	Yes	
	Abbvie	NCT00647920	Yes	Yes	
	Abbvie	NCT00538902	Yes	Yes	
	Abbvie	NCT00647270	Yes	Yes	
	Abbvie	DE031- No NCT	Yes	Yes	
	Abbvie	NCT00870467	Yes	Yes	
	Pfizer	NCT00853385	No	No	
	Pfizer	NCT00550446	No	No	
	Detert	PMID 22739990	Yes	Yes	
Etanercept	Amgen	PMID : 9920948	Yes	Yes	
	Amgen	PMID 14872476	Yes	No	Study conducted over 16 weeks, with only the first 8 weeks with a placebo group
	Amgen	NCT01313208	Yes	Yes	
	Pfizer	NCT00445770	Yes	Yes	
	Pfizer	NCT00565409	Yes	No	First 16 weeks realized in open-label
	Pfizer	NCT00913458	Yes	No	First 52 weeks realized in open-label
	Pfizer	NCT00858780	Yes	No	Open-label ETN 50mg treatment for 8 weeks prior to randomization
	Emery		No	No	
Certolizumab	UCB	NCT00160602	Yes	Yes	
	UCB	NCT00152386	Yes	Yes	
	UCB	NCT00717236	Yes	Yes	
	UCB	NCT00548834	Yes	Yes	
	UCB	NCT00175877	Yes	No	Single CZP arm in open-label
	Astellas	NCT01451203	No	No	
	UCB	NCT00674362	Yes	Yes	
	UCB	NCT00580840	Yes	No	First 16 weeks realized in open-label
	UCB	NCT01235598	Yes	No	Presence of a placebo group only during the first 4 weeks
	UCB	NCT01519791	Yes	Yes	

Supplemental document 3 Characteristics of included studies

Registration/ Protocole	Sponsor	Period	Drug	Patients	Design	Sites	Randomized patients	Follow up	Primary outcome
NCT00647491/ VIV0000303	Abbvie	2004-2005	ADA	Active RA	4 arms: ADA 20mgSc eow, ADA 40mgSc eow, ADA80mgSc eow, PLB eow	Japan	352	24 weeks	ACR 20 Week 24
NCT00420927/ VIV0000301 OPTIMA	Abbvie	2006-2010	ADA	Early RA	2 arms in period 1: ADA40mg+MTX eow, PLB+MTX eow	US, South America, Europe,	1032	78 weeks	DAS28, Sharp Week78
NCT00195663/ VIV0000296 PREMIER	Abbvie	2000-2012	ADA	Early RA, naïve from DMARD	3 arms: ADA 40mgSc/2W ADA 40mg/2W+MTX PLB+MTX	Australia, Canada, Europe, US	799	10 years	ACR50, Sharp Week52
NCT00195702/ VIV0000296	Abbvie	2000-2010	ADA	Active RA despite MTX	3 arms: ADA20mg eow + MTX ADA40mg/2w+MTX PLB+ MTX	US, Canada	619	10 years	ACR20 W24, Sharp W52, HAQ W52,
NCT00234845/ VIV00002980	Abbvie	2003- 2005	ADA	Early RA, naïve from DMARD	2 arms: ADA40mg/2w+ MTX PLB eow + MTX	US	148	60 weeks	Job loss measurement
NCT00235859/ VIV00002986	Abbvie	2003- 2005	ADA	Active RA despite MTX	2 arms: ADA40mgSC/2w+ MTX PLB/2w + MTX	South Korea	128	24 weeks	ACR20 Week 24
NCT00647920/ VIV00003035	Abbvie	2003- 2005	ADA	Active RA despite MTX	2 arms: ADA40mgSC/2w+ MTX PLB/2w+ MTX	Taiwan (single center)	47	12 weeks	ACR20 Week 12
NCT00538902/ VIV00003021	Abbvie	2007-2009	ADA	Active RA	3 arms: ADA 80mgSC/2w+MTX ADA 40mgSC/2w+MTX PLB/2w +MTX	China	302	12 weeks	ACR20 Week 12
NCT00647270/ VIV00003032	Abbvie	2007-2009	ADA	Active RA	3 arms: ADA 80mg/4w ADA 40mg/2w PLB (12 weeks only)	US, Australia, Canada, Europe, Puerto Rico	420	24 weeks	ACR20 Week 12
PMID14719195 DE031 STAR	Abbvie	2003	ADA	Active RA	2 arms: ADA 40mg/2w PLB/2w	US, Canada	636	24 weeks	Incidence of adverse events
NCT00870467/ VIV00003053	Abbvie	2009-2011	ADA	Early RA, naive from MTX and TNF inhibitors	2 arms: ADA40mg/2w + MTX PLB/2w + MTX	Japan	334	52 weeks	Sharp Week 26
PMID 22739990 / HIT HARD	Detert	2012	ADA	Active early RA, naïve from DMARD	2 arms ADA40mg/2w + MTX PLB/2W +MTX	Europe	172	48 weeks	DAS 28 Week 48

ACR = American College of Rheumatology, TNF inhibitors= anti-tumor necrosis factor, ADA= adalimumab, MTX= methotrexate, PLB= placebo, RA= rheumatoid arthritis.

Supplemental document 3 Characteristics of included studies

Registration / Protocol	Sponsor	Period	Drug	Patients	Design	Sites	Randomized patients	Duration	Primary outcome
PMID 9920948/ 160014	Amgen	1998	ETN	Active RA despite MTX	2 arms: ETN 25mgx2/w + MTX PLB x2/w + MTX	US	89	24 weeks	ACR20 Week 24
NCT01313208/ 20070561	Amgen	2011-2013	ETN	Moderate RA despite MTX	2 arms: (12 weeks only) ETN 50mg/w +DMARDS PLB/w + DMARDS	US, Canada	210	24 weeks	DAS28 Week 12
NCT00445770/ B1801002	Pfizer	2006-2011	ETN	RA, naive from TNF inhibitors	3 arms: ETN 10mg x2/w ENT25mg x2/w MTX 8mg/w	Japan	550	52 weeks	Sharp Week 52
NCT00160602/ C87050	UCB	2005-2006	CZP	Patients with active RA despite MTX, naive from TNF inhibitors	3 arms: CZP400mg+MTX CZP200mg+MTX PLB + MTX	US, Europe, South America, Israel, Russia	590	24 weeks	ACR 20 Week 24
NCT00152386/ C87027	UCB	2005-2006	CZP	Patients with active RA despite MTX, naive from TNF inhibitors	3 arms: CZP400mg/2w +MTX CZP200mg/2w +MTX PLB +MTX	US, South America, Australia, Europe, Israel, Russia	950	52 weeks	ACR 20 Week 24
NCT00717236/ C87094 REALISTIC	UCB	2008-2011	CZP	Patients with active RA despite MTX, naive from TNF inhibitors	2 arms: CZP 400mg/2w +DMARD PLB +DMARD	US, Canada, Europe	1648	12 weeks then extension	ACR 20 Week 12
NCT00548834/ C87011	UCB	2003-2004	CZP	Patients with active RA despite DMARD, naive from TNF inhibitors	2 arms: (csDMARD prohibited) CZP400mg/4w PLB/4w	US, Europe,	220	24 weeks	ACR 20 Week 24
NCT00674362/ C87076 CERTAIN	UCB	2008-2010	CZP	Patients with moderate to low disease activity RA	2 arms: CZP200mg/2w + DMARDs PLB + DMARDs	Europe	194	52 weeks	CDAI Weeks 20, 24
NCT01519791/ RA0055Period1 C-EARLY	UCB	2012-2015	CZP	Patients with early active RA, naïve from DMARD	2 arms: CTZ200mg/2w + MTX PLB + MTX	US, South America, Australia, Europe	880	52 weeks	DAS remission Week 52

ACR = American College of Rheumatology, TNF inhibitors= anti-tumor necrosis factor, ETN= etanercept, CZP = certolizumab, MTX= methotrexate, PLB= placebo, RA= rheumatoid arthritis.

Supplemental document 3 Characteristics of included studies

Registration / Protocol	Sponsor	Period	Drug	Patients	Design	Sites	Randomized patients	Duration	Primary outcome
C0524T05/ NCT00264537/ Go-Before	Centocor	2005-2008	GOL	Active RA naive from MTX and TNF inhibitors	4 arms: PLB + MTX, GOL 10Mg/4W, GOL 50mg/4W+MTX, GOL 100mg/4W+MTX	USA, Canada, South America, Australia, Europe, India, Thailand, Korea, Taiwan	637	52 weeks	ACR50 Week 24
C0524T06/ NCT00264550/ Go-Forward	Centocor	2005-2008	GOL	Active RA despite MTX	4 arms: PLB + MTX, GOL 10Mg/4W, GOL 50mg/4W+MTX, GOL 100mg/4W+MTX	USA, Canada, South America, Australia, Europe, Taiwan	444	52 weeks	ACR20 Week 14
C0524T11/ NCT00299546 / Go-After	Centocor	2005-2007	GOL	Active RA previously treated with TNF inhibitors	3 arms: PLB, GOL 50mg/4W, GOL 100mg/4W (concomitant treatment by MTX, sulfasalazine or hydroxychloroquine is permitted but not required)	USA, Canada, Europe, Australia, New Zealand	461	24 weeks	ACR20 Week 14
C0524T12/ NCT00361335/ Go-Live	Centocor	2006-2008	GOL	Active RA despite MTX	5 arms: PLB/12W+ MTX, GOL 2mg/kg/12W+MTX, GOL 2mg/kg/12W+PLB, GOL 4mg/kg/12W+MTX, GOL 4mg/kg/12W+PLB	USA, Australia, Europe, South America, Malaysia	643	48 weeks	ACR50 Week 14
CNTO148ART3001/ NCT00973479/ Go-Further	Centocor	2009-2011	GOL	Active RA despite MTX	2 arms: PLB + MTX, GOL 2mg/kg+ MTX	USA, South America, Australia, Europe, Korea, Malaysia, Russia, New Zealand	592	100 weeks	ACR20 Week 14
C0524T28 /NCT01248780	Centocor	2010-2013	GOL	Active RA despite MTX	2 arms: PLB + MTX, GOL 50mg/4W + MTX	China	264	48 weeks	ACR20 Week 14
C0168T22/ NCT00269867/ ATTRACT	Centocor	1997-1998	INF	active RA despite MTX	5 arms: PLB+MTX, INF 3mg/kg/8W+MTX, INF 3mg/kg/4W+MTX, INF 10mg/kg/8W+MTX, INF 10mg/kg/4W+MTX	-	428	54 weeks	ACR20 Week 30
C0168T29/ NCT00236028/ ASPIRE	Centocor	2000-2003	INF	Patients with active RA from 3 month to 3 years, naive from MTX and TNF inhibitors	3 arms: PLB+MTX, INF 3mg/kg/8W+MTX, INF 6mg/kg/8W + MTX (weeks 0,2, 6 and then every 8 weeks)	-	1049	58 weeks	ACR20,30, 50 Week 54 ACR50 Week 24

ACR American College of Rheumatology, TNF inhibitors= anti-tumor necrosis factor, GOL= golimumab, INF = infliximab, MTX= methotrexate, PLB= placebo, RA= rheumatoid arthritis

Supplemental document 4: Mean difference of final DAS28(CRP) between TNF inhibitors and placebo by clinical and biological baseline characteristics.

	Number of studies	Number of patients		Mean Difference (95% CI)	Heterogeneity		p for subgroup difference
		TNF inhibitors	Placebo		I^2 (%)	*p*	
Smoking							
Yes	14	1409	685	-0.42 [-0.63 ; -0.22]	50	0.02	0.77
No		2329	1070	-0.47 [-0.64 ; -0.29]	65	< 0.01	
Physical activity							
Yes	5	297	138	-0.25 [-0.54 ; 0.03]	0	0.86	0.58
No		1488	610	-0.36 [-0.58 ; -0.13]	52	0.08	
Gender							
Women	27	5585	2513	-0.56 [-0.70 ; -0.43]	75	< 0.01	0.64
Men		1526	689	-0.51 [-0.68 ; -0.34]	30	0.08	
Age							
>50	27	4760	1876	-0.51 [-0.63 ; -0.38]	60	< 0.01	0.15
<=50		3315	1407	-0.65 [-0.81 ; -0.50]	64	< 0.01	
BMI							
>= 30	28	2125	828	-0.48 [-0.59 ; -0.37]	0	0.63	0.12
< 30		5977	2492	-0.62 [-0.77 ; -0.48]	78	< 0.01	
RF status							
Positive	28	6480	2668	-0.61 [-0.75 ; -0.47]	78	< 0.01	0.28
Negative		1425	559	-0.50 [-0.64 ; -0.35]	14	0.27	
ACPA status							
Positive	13	3058	1462	-0.44 [-0.66 ; -0.22]	83	< 0.01	0.99
Negative		920	368	-0.44 [-0.67 ; -0.21]	38	0.09	
Disease duration							
< 2 years	22	2781	1416	-0.52 [-0.70 ; -0.34]	60	< 0.01	**0.07**
2-10 years		1104	535	-0.39 [-0.57 ; -0.21]	26	0.15	
=>10 years		688	333	-0.78 [-1.05 ; -0.50]	40	0.07	
Baseline DAS28							
> 5.1	27	6097	2344	-0.61 [-0.75 ; -0.47]	75	< 0.01	0.44
<= 5.1		1948	899	-0.53 [-0.67 ; -0.39]	56	< 0.01	

ACPA = Anti-citrullinated protein antibodies, Baseline DAS28 = DAS28(CRP) score at baseline, BMI = Body Mass Index, RF= Rheumatoid factors.

Supplemental document 5: Odds-Ratios of good EULAR response of TNF inhibitors versus placebo, by clinical and biological baseline characteristics.

	Number of studies	Number of patients		Odds-Ratios (Peto, fixed, 95% CI)	Heterogeneity		p for subgroup difference
		TNF inhibitors	Placebo		I^2 (%)	p	
Smoking							
Yes	14	1409	685	1.93 [1.42 ; 2.61]	38	0.08	0.95
No		2329	1070	1.95 [1.43 ; 2.67]	63	< 0.01	
Physical activity							
Yes	5	297	138	1.52 [0.89 ; 2.59]	11	0.34	0.87
No		1191	472	1.60 [1.12 ; 2.29]	41	0.15	
Gender							
Women	27	5585	2513	2.14 [1.80 ; 2.55]	47	< 0.01	0.50
Men		1526	689	1.95 [1.58 ; 2.40]	0	0.84	
Age							
>50	27	4760	1876	2.03 [1.71 ; 2.41]	30	0.07	0.59
<=50		3315	1407	2.17 [1.81 ; 2.60]	20	0.18	
BMI							
>= 30	28	2125	828	1.87 [1.49 ; 2.36]	7	0.37	0.22
< 30		5977	2492	2.24 [1.88 ; 2.68]	49	< 0.01	
RF status							
Positive	27	6480	2668	2.19 [1.83 ; 2.62]	51	< 0.01	0.61
Negative		1425	559	2.01 [1.54 ; 2.63]	3	0.42	
ACPA status							
Positive	13	3058	1462	2.00 [1.58 ; 2.54]	52	0.01	0.79
Negative		920	368	2.12 [1.51 ; 2.97]	2	0.43	
Disease duration							
< 2 years	22	2781	1416	1.95 [1.69 ; 2.24]	0	0.69	0.69
2-10 years		1104	535	2.14 [1.62 ; 2.81]	0	0.46	
=>10 years		688	333	1.65 [0.94 ; 2.91]	40	0.05	
Baseline DAS28							
> 5.1	27	6097	2344	2.19 [1.77 ; 2.72]	53	< 0.01	0.73
<= 5.1		1948	899	2.32 [1.86 ; 2.89]	23	0.14	

ACPA = Anti-citrullinated protein antibodies, Baseline DAS28 = DAS28(CRP) score at baseline, BMI = Body Mass Index, RF= Rheumatoid factors.

Supplemental document 6: Odds-Ratios of EULAR non-response of TNF inhibitors versus placebo, by clinical and biological baseline characteristics.

	Number of studies	Number of patients		Odds-Ratios (Peto, fixed, 95% CI)	Heterogeneity		p for subgroup difference
		TNF inhibitors	Placebo		I^2 (%)	*p*	
Smoking							
Yes	14	1409	685	0.44 [0.33 ; 0.59]	25	0.19	0.97
No		2329	1070	0.44 [0.34 ; 0.59]	51	0.01	
Physical activity							
Yes	5	297	138	0.57 [0.36 ; 0.89]	0	0.59	0.95
No		1191	472	0.58 [0.45 ; 0.74]	15	0.32	
Gender							
Women	27	5585	2513	0.40 [0.33 ; 0.49]	60	< 0.01	0.94
Men		1526	689	0.41 [0.31 ; 0.53]	10	0.32	
Age							
>50	27	4760	1876	0.43 [0.35 ; 0.53]	45	< 0.01	0.34
<=50		3315	1407	0.38 [0.31 ; 0.46]	23	0.15	
BMI							
>= 30	28	2125	828	0.52 [0.43 ; 0.63]	0	0.97	**0.01**
< 30		5977	2492	0.36 [0.30 ; 0.45]	62	< 0.01	
RF status							
Positive	27	6480	2668	0.38 [0.31 ; 0.46]	58	< 0.01	0.13
Negative		1425	559	0.48 [0.38 ; 0.61]	0	0.83	
ACPA status							
Positive	13	3058	1462	0.42 [0.31 ; 0.57]	69	< 0.01	0.29
Negative		920	368	0.52 [0.39 ; 0.70]	0	0.51	
Disease duration							
< 2 years	22	2781	1416	0.44 [0.33 ; 0.58]	44	0.02	0.33
2-10 years		1104	535	0.52 [0.38 ; 0.71]	29	0.13	
=>10 years		688	333	0.35 [0.23 ; 0.54]	31	0.12	
Baseline DAS28							
> 5.1	27	6097	2344	0.42 [0.35 ; 0.51]	53	0.01	0.31
<= 5.1		1948	899	0.36 [0.27 ; 0.47]	39	0.02	

ACPA = Anti-citrullinated protein antibodies, Baseline DAS28 = DAS28(CRP) score at baseline, BMI = Body Mass Index, RF= Rheumatoid factors.

Supplemental document 7: Differences in final TJC28, SJC28, PGA and CRP between TNF inhibitors and placebo

		TJC28			SJC28			PGA			CRP		
Sub-groups	Studies	I^2 (%)	Mean Difference (95% CI)	*p*	I^2 (%)	Mean Difference (95% CI)	*p*	I^2 (%)	Mean Difference (95% CI)	*p*	I^2 (%)	Mean Difference (95% CI)	*p*
Smoking													
Yes	14	40	-1.18 [-2.04 ; -0.32]	0.93	32	-1.09 [-1.64 ; -0.54]	0.91	39	-4.65 [-7.83 ; -1.47]	0.83	2	-2.38 [-3.89 ; -0.87]	0.33
No		45	-1.23 [-1.85 ; -0.61]		77	-1.14 [-1.83 ; -0.46]		44	-4.20 [-6.66 ; -1.74]		32	-3.49 [-5.13 ; -1.85]	
PA													
Yes	5	0	-0.26 [-1.57 ; 1.05]	0.17	0	-0.48[-1.40 ; 0.43]	0.31	0	-5.46 [-10.79 ; -0.14]	0.42	0	-3.06 [-5.80 ; -0.32]	0.30
No		0	-1.31 [-2.07 ; -0.55]		0	-1.03[-1.57 ; -0.50]		16	-2.93 [-5.99 ; 0.14]		46	-0.79 [-4.14 ; 2.55]	
Gender													
Women	27	58	-1.52 [-2.01 ; -1.04]	0.70	79	-1.63 [-2.14 ; -1.12]	0.56	70	-5.85 [-8.02 ; -3.69]	0.45	52	-3.92 [-5.12 ; -2.71]	0.37
Men		13	-1.68 [-2.32 ; -1.04]		17	-1.42 [-1.93 ; -0.91]		33	-4.48 [-7.31 ; -1.65]		32	-2.93 [-4.72 ; -1.14]	
Age													
>50	27	49	-1.47 [-1.97 ; -0.96]	0.25	77	-1.64 [-2.19 ; -1.08]	0.55	25	-4.13 [-6.66 ; -1.60]	0.13	37	-4.01 [-5.20 ; -2.82]	0.68
<=50		52	-1.93 [-2.53 ; -1.32]		69	-1.88 [-2.45 ; -1.31]		74	-6.72 [-8.96 ; -4.48]		65	-4.46 [-6.28 ; -2.64]	
BMI													
>=30	28	0	-1.35[-1.92 ; -0.79]	0.19	12	-1.28 [-1.75 ; -0.81]	**0.07**	61	-5.05 [-7.20 ; -2.90]	0.31	22	-3.56 [-5.02 ; -2.10]	0.39
<30		69	-1.88[-2.43 ; -1.32]		81	-1.93 [-2.45 ; -1.40]		62	-6.79 [-9.35 ; -4.23]		63	-4.43 [-5.77 ; -3.10]	
RF													
Positive	28	69	-1.83 [-2.37 ; -1.30]	0.43	83	-1.93 [-2.48 ; -1.37]	0.11	73	-6.24 [-8.43 ; -4.05]	0.57	67	-4.66 [-6.15 ; -3.18]	**<0.01**
Négative		25	-1.45 [-2.24 ; -0.65]		22	-1.30 [-1.85 ; -0.74]		31	-5.19 [-8.07 ; -2.31]		1	-2.02 [-3.00 ; -1.05]	
ACPA													
Positive	13	75	-1.32[-2.13 ; -0.50]	0.83	83	-1.17 [-1.89 ; -0.44]	0.54	74	-4.96 [-8.15 ; -1.76]	0.95	63	-2.66 [-4.58 ; -0.74]	0.24
Négative		10	-1.18[-2.08 ; -0.28]		43	-0.82 [-1.66 ; 0.02]		14	-4.82 [-8.26 ; -1.38]		29	-4.53 [-7.01 ; -2.05]	
Duration													
< 2 years	22	62	-1.63 [-2.45 ; -0.81]	**< 0.01**	65	-1.14 [-1.78 ; -0.50]	**0.07**	57	-4.62 [-7.51 ; -1.74]	0.90	39	-3.46 [-5.01 ; -1.91]	0.39
2-10 years		0	-1.04 [-1.75 ; -0.32]		0	-1.38 [-1.96 ; -0.81]		18	-5.22 [-8.08 ; -2.37]		27	-2.93 [-4.57 ; -1.28]	
>=10 years		0	-3.21 [-4.16 ; -2.26]		45	-2.75 [-3.96 ; -1.55]		63	-6.08 [-11.86 ; -0.30]		58	-5.41 [-8.52 ; -2.29]	
DAS28(CRP)													
>5.1	27	64	-1.95 [-2.52 ; -1.37]	**0.07**	77	-2.10 [-2.66 ; -1.54]	**< 0.01**	68	-5.80 [-7.95 ; -3.64]	0.60	60	-4.69 [-6.22 ; -3.16]	**0.04**
<=5.1		39	-1.29 [-1.72 ; -0.86]		53	-0.90 [-1.27 ; -0.52]		57	-6.73 [-9.48 ; -3.99]		40	-2.72 [-3.86 ; -1.59]	

TJC28 =Tender joint count, SJC28: Swollen joint count; PGA: Patient Global assessment; PA Physical Activity; RF Rheumatoid factor;

Supplemental document 8: Mean difference of ΔTJC28, ΔSJC28, ΔPGA, ΔCRP between TNF inhibitors and placebo

		ΔTJC28			Δ SJC28			Δ PGA			Δ CRP		
Sub-groups	Studies	I^2 (%)	Mean Difference (95% CI)	*p*	I^2 (%)	Mean Difference (95% CI)	*p*	I^2 (%)	Mean Difference (95% CI)	*p*	I^2 (%)	Mean Difference (95% CI)	*p*
Smoking													
Yes	14	30	-1.57 [-2.42 ; -0.71]	0.72	0	-1.25 [-1.77 ; -0.72]	0.95	0	-7.39 [-10.07 ; -4.72]	0.26	28	-3.14 [-6.14 ; -0.14]	0.82
No		45	-1.37 [-2.05 ; -0.68]		47	-1.27 [-1.80 ; -0.74]		50	-5.10 [-8.06 ; -2.13]		24	-3.57 [-5.72 ; -1.42]	
PA													
Yes	5	0	-1.30 [-2.65 ; 0.04]	0.60	0	-0.88 [-1.88 ; 0.11]	0.66	0	-6.92 [-13.04 ; -0.81]	0.54	0	-4.44 [-8.09 ; -0.79]	0.40
No		3	-1.72 [-2.46 ; -0.98]		0	-1.13 [-1.66 ; -0.60]		31	-4.70 [-8.28 ; -1.11]		47	-2.21 [-5.86 ; 1.45]	
Gender													
Women	27	57	-1.78 [-2.31 ; -1.25]	0.49	66	-1.80 [-2.26 ; -1.33]	0.20	57	-7.65 [-9.76 ; -5.54]	0.64	39	-4.82 [-6.28 ; -3.37]	0.32
Men		30	-1.43 [-2.27 ; -0.58]		0	-1.34 [-1.86 ; -0.82]		29	-6.74 [-9.89 ; -3.60]		0	-3.30 [-5.92 ; -0.69]	
Age													
>50	27	56	-1.49 [-2.09 ; -0.89]	0.14	64	-1.70 [-2.21 ; -1.18]	0.48	46	-6.76 [-8.89 ; -4.63]	0.22	37	-4.82 [-6.66 ; -2.97]	0.69
<=50		22	-2.08 [-2.59 ; -1.57]		45	-1.95 [-2.44 ; -1.46]		25	-8.63 [-10.69 ; -6.56]		14	-5.31 [-6.89 ; -3.72]	
BMI													
>=30	28	19	-1.61 [-2.29 ; -0.92]	0.46	27	-1.66 [-2.23 ; -1.09]	0.42	0	-6.18 [-8.49 ; -3.87]	0.23	0	-4.26 [-5.92 ; -2.59]	0.44
<30		62	-1.94 [-2.50 ; -1.38]		72	-1.98 [-2.48 ; -1.47]		64	-8.15 [-10.39 ; -5.92]		47	-5.20 [-6.90 ; -3.50]	
RF													
Positive	28	59	-1.86 [-2.38 ; -1.34]	0.44	69	-2.00 [-2.48 ; -1.53]	0.12	51	-8.40 [-10.29 ; -6.50]	0.13	28	-5.58 [-7.02 ; -4.14]	**0.06**
Négative		10	-1.50 [-2.27 ; -0.72]		40	-1.32 [-2.05 ; -0.60]		0	-5.87 [-8.49 ; -3.25]		41	-2.53 [-5.34 ; 0.28]	
ACPA													
Positive	13	72	-1.52 [-2.36 ; -0.67]	0.62	77	-1.38 [-2.11 ; -0.65]	0.83	48	-6.65 [-9.29 ; -4.01]	0.23	52	-4.76 [-7.27 ; -2.25]	0.24
Négative		0	-1.82 [-2.70 ; -0.94]		32	-1.26 [-2.10 ; -0.41]		0	-3.94 [-7.44 ; -0.43]		24	-1.97 [-5.89 ; 1.96]	
Duration													
< 2 years	22	51	-1.63 [-2.45 ; -0.80]	0.10	49	-1.23 [-1.87 ; -0.59]	0.11	44	-4.55 [-7.67 ; -1.43]	0.17	0	-3.43 [-5.21 ; -1.64]	0.83
2-10 years		24	-1.37 [-2.25 ; -0.49]		9	-1.37 [-2.00 ; -0.74]		30	-8.25 [-11.67 ; -4.83]		3	-4.29 [-6.46 ; -2.13]	
>=10 years		3	-2.77 [-3.77 ; -1.77]		49	-2.71 [-3.97 ; -1.45]		64	-9.59 [-15.64 ; -3.53]		45	-4.04 [-8.08 ; -0.01]	
DAS28CRP													
>5.1	27	54	-1.92 [-2.47 ; -1.37]	**0.07**	69	-2.11 [-2.66 ; -1.56]	**< 0.01**	56	-7.25 [-9.34 ; -5.16]	0.59	41	-5.56 [-7.43 ; -3.69]	**0.05**
<=5.1		50	-1.19 [-1.74 ; -0.64]		25	-1.05 [-1.41 ; -0.70]		22	-8.11 [-10.41 ; -5.81]		29	-3.36 [-4.58 ; -2.15]	

TJC28 =Tender joint count, SJC28: Swollen joint count; PGA: Patient Global assessment; PA Physical Activity; RF Rheumatoid factor;

Supplemental document 9: Intervals adaptation for the categories "age" and "disease duration" for Certolizumab studies.

	Age	
	<=50 years	>50 years
NCT00160602	(<49)	**(49-62)** (>62)
NCT00152386	(18-47)	**(48-55)** (56-63) (>63)
NCT00717236	(18-47)	**(48-55)** (56-62) (>62)
NCT00548834	(<45)	**(45-<56)** (56-<65) (>65)
NCT00674362	(<49)	**(49-59)** (>59)
NCT01519791	(<42) (42-48)	**(49-55)** (56-62) (63-69) (>69

	Disease duration		
	<2 years	Between 2 et 10 years	>10 years
NCT00160602	**(<=3)**	**(>3)**	
NCT00152386	**(<=3)**	**(>3)**	
NCT00717236	(<2)	**(>=2)**	
NCT00674362	(<2)	**(>=2)**	

*In bold the intervals where patients may have been misclassified.

Supplemental document 10: Final EULAR response and disease activity in TNF inhibitors groups

Studies	Arm	Number analyzed	Week of assessment	Good response (%)	Intermediate response (%)	Non response (%)	Mean final TJC28 (sd)	Mean final SJC28 (sd)	Mean final PGA (sd)	Mean final CRP (mg/l) (sd)	Mean final DAS28CRP (sd)
NCT00647491	Adalimumab	235	24	17	45.5	37.4	8.31 (7.38)	7.82 (5.99)	44.97 (26.71)	34.17 (33.11)	4.8 (1.53)
NCT00420927	Adalimumab	433	26	52.7	37.6	9.7	5.12 (6.37)	3.43 (4.72)	24.73 (23.48)	7.18 16.99	3.23 (1.38)
NCT00195663	Adalimumab	427	24	39.3	49.2	11.5	5.6 (6.78)	4.68 (5.44)	24.72 (25.03)	13.79 (22)	3.6 (1.45)
NCT00195702	Adalimumab	345	24	41.2	47	11.9	4.64 (5.79)	5.14 (5.12)	22.44 (19.85)	9.12 (5.02)	3.57 (1.16)
NCT00234845	Adalimumab	53	24	66	26.4	7.5	2.64 (4.37)	1.92 (3.87)	16.72 (18.75)	5.36 (5.84)	2.66 (1.15)
NCT00235859	Adalimumab	59	24	59.3	28.8	11.9	4.31 (4.5)	2.14 (3.12)	33.54 (22.51)	6.85 (22.95)	3.14 (1.19)
NCT00647920	Adalimumab	32	12	18.8	50	31.3	9.12 (8.1)	5.97 (6.75)	52.69 (21.78)	13.51 (32.92)	4.27 (1.57)
NCT00538902	Adalimumab	223	12	26.5	52	21.5	7.48 (7.12)	3.33 (4.2)	41.07 (21.25)	9.75 (16.56)	3.89 (1.28)
NCT00647270	Adalimumab	296	24	26.7	44.9	28.4	8.86 (8.37)	6.36 (6.2)	36.28 (24.71)	7.69 (11.24)	4.12 (1.4)
DE31	Adalimumab	288	24	31.9	46.2	21.9	6.36 (7.1)	7.3 (6.56)	28.98 (23.54)	8.85 (13.95)	3.84 (1.38)
NCT00870467	Adalimumab	144	26	51.4	43.8	4.9	3.15 (5)	2.48 (3.32)	17.87 (17.99)	5.85 (14.15)	2.64 (1.22)
PMID 22739990	Adalimumab	73	24	61.6	32.9	5.5					
PMID9920948	Etanercept	43	24	27.9	62.8	9.3	4.28 (3.97)	5.28 (4.8)	27.67 (20.22)	12.6 (20.06)	3.57 (1.05)
NCT01313208	Etanercept	98	24	30.6	39.8	29.6				4.21 (6.31)	
NCT00445770	Etanercept	325	24	46.2	45.8	8	2.81 (3.42)	2.64 (3.03)	24.66 (19.88)	4.58 (8.99)	2.81 (1.17)
NCT00160602	Certolizumab	351	24	27.4	67.8	4.8	4.93 (4.99)	3.33 (3.72)	30.28 (19.5)	10.25 (15.97)	3.49 (1.11)
NCT00152386	Certolizumab	545	24	32.1	63.1	4.8	4.53 (4.94)	3.15 (3.87)	26.54 (19.88)	10.03 (16.96)	3.39 (1.14)
NCT00717236	Certolizumab	754	12	21.9	53.3	24.8	6.96 (7)	5.15 (5.13)	36.41 (25.25)	9.71 (18.2)	3.92 (1.33)
NCT00548834	Certolizumab	75	24	18.7	54.7	26.7	5.56 (5.9)	5.88 (5.51)	24.13 (9.02)	13.73 (24.35)	3.71 (1.16)
NCT00674362	Certolizumab	76	24	36.8	40.8	22.4	2.96 (3.96)	1.68 (1.79)	26.13 (21.78)	8.02 (15.11)	3.01 (0.99)
NCT01519791	Certolizumab	649	24	44.8	46.4	8.8	4.07 (5.62)	2.6 (3.81)	22.92 (23.48)	7.56 (20.22)	2.94 (1.33)
NCT00264537	Golimumab	422	24	38.6	39.3	22	6.82 (7.7)	4.48 (5.29)	34.66 (26.36)	10.86 (22.72)	3.76 (1.55)
NCT00264550	Golimumab	282	24	34.8	40.1	25.2	6.56 (7.08)	4.12 (4.82)	34.8 (25.36)	11.08 (20.5)	3.78 (1.41)
NCT00299546	Golimumab	223	24	21.5	43.9	34.5	8.82 (8.08)	5.91 (5.72)	41.32 (27.26)	12.38 (24.59)	4.25 (1.53)
NCT00361335	Golimumab	449	24	16.9	40.8	42.3	8.85 (7.41)	6.19 (5.4)	43.67 (27)	16.04 (22.4)	4.49 (1.4)
NCT00973479	Golimumab	362	24	39.5	47.8	12.7	4.72 (4.4)	2.73 (3.25)	36.27 (21.72)	10.46 (17.78)	3.54 (1.17)
NCT01248780	Golimumab	112	24	31.3	40.2	28.6	4.9 (4.54)	2.41 (2.9)	46.27 (24.63)	11.07 (17.48)	3.6 (1.36)
NCT00269867	Infliximab	225	30	31.1	47.6	21.3	7.15 (7.73)	7.08 (6.44)	33.88 (24.87)	11.93 (17.26)	4.03 (1.51)
NCT00236028	Infliximab	617	30	43.8	43.8	12.5	5.51 (6.73)	4.6 (5.03)	27.29 (25.39)	7.81 (14)	3.53 (1.34)

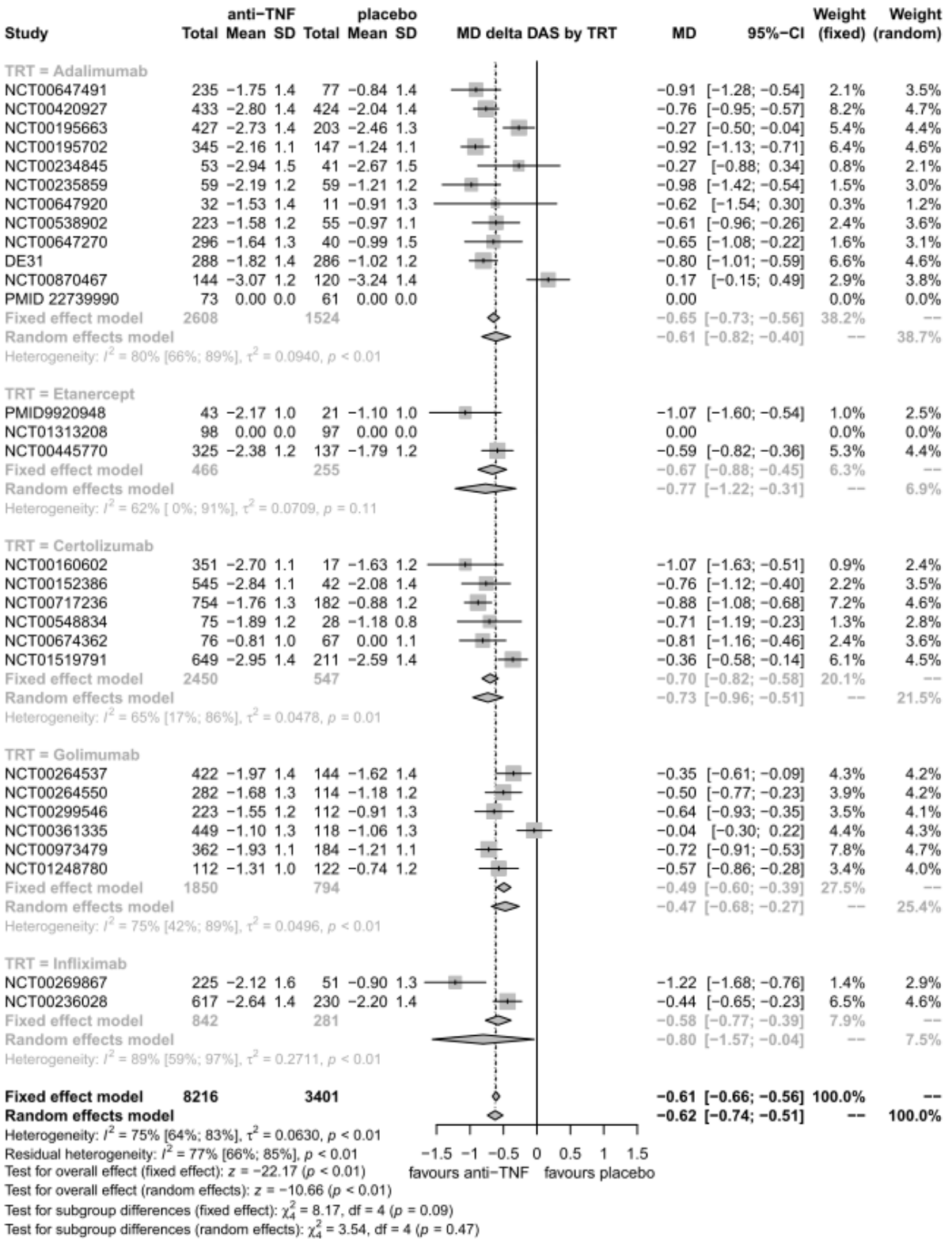
TJC28 =Tender joint count, SJC28: Swollen joint count; PGA: Patient Global assessment.

Supplemental document 11: Final EULAR response and disease activity in Placebo groups

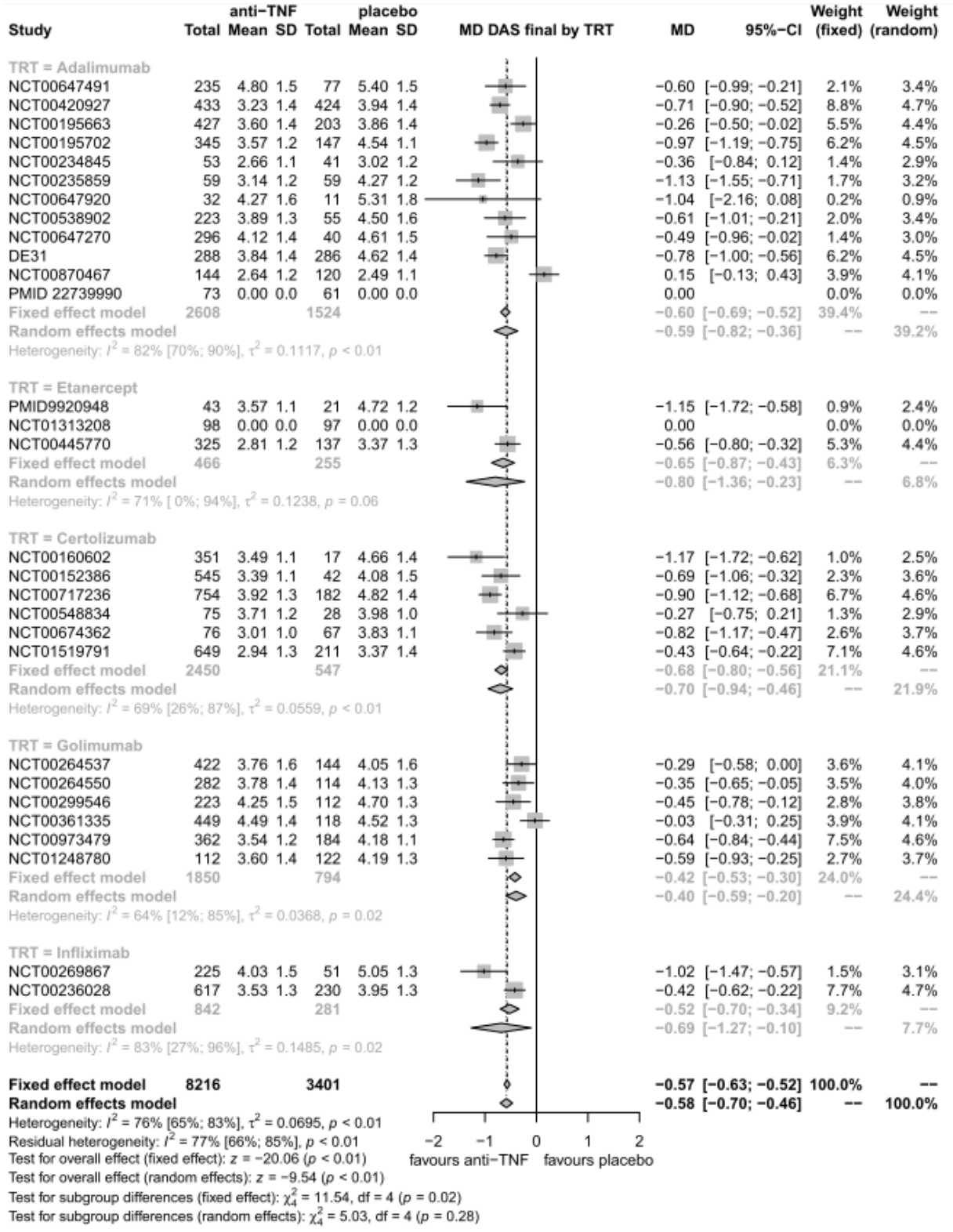
Studies	Arm	Number analyzed	Week of assessment	Good response (%)	Intermediate response (%)	Non response (%)	Mean final TJC28 (sd)	Mean final SJC28 (sd)	Mean final PGA (sd)	Mean final CRP (mg/l) (sd)	Mean final DAS28CRP (sd)
NCT00647491	Placebo	77	24	7.8	31.2	61	10.56 (7.58)	10.1 (6.15)	52.31 (25.03)	42.62 (34.13)	5.4 (1.46)
NCT00420927	Placebo	424	26	30.4	47.9	21.7	7.1 (6.95)	5.26 (5.58)	33.41 (24.48)	11.1 (16.3)	3.94 (1.43)
NCT00195663	Placebo	203	24	28.1	57.6	14.3	6.19 (6.49)	6.14 (5.77)	23.74 (21.88)	14.43 (19.45)	3.86 (1.36)
NCT00195702	Placebo	147	24	12.2	57.1	30.6	7.93 (6.75)	8.65 (6.3)	36.73 (22.98)	14.7 (15.99)	4.54 (1.15)
NCT00234845	Placebo	41	24	48.8	39	12.2	3.9 (5.08)	2.54 (4.06)	17.44 (19.95)	7.32 (8.88)	3.02 (1.21)
NCT00235859	Placebo	59	24	15.3	50.8	33.9	7.02 (4.77)	5.17 (3.69)	45.14 (24.41)	13.88 (19.09)	4.27 (1.16)
NCT00647920	Placebo	11	12	9.1	27.3	63.6	11.91 (10.08)	10.36 (7.85)	64.91 (18.4)	21.55 (24.89)	5.31 (1.83)
NCT00538902	Placebo	55	12	23.6	30.9	45.5	10.51 (8.88)	4.98 (5.82)	45.24 (22.74)	16.25 (21.12)	4.5 (1.59)
NCT00647270	Placebo	40	24	17.5	42.5	40	9.9 (9.24)	8.82 (7.48)	39.17 (23.99)	15.45 (20.56)	4.61 (1.5)
DE31	Placebo	286	24	17.1	34.6	48.3	9.14 (7.82)	9.74 (7.04)	41.13 (24.44)	12.45 (14.55)	4.62 (1.36)
NCT00870467	Placebo	120	26	36.7	29.2	34.2	1.96 (3.34)	1.35 (2.64)	14.93 (17.97)	9.84 (14.05)	2.49 (1.11)
PMID 22739990	Placebo	61	24	47.5	41	11.5					
PMID9920948	Placebo	21	24	4.8	61.9	33.3	7.86 (6.57)	8.95 (6.48)	42.86 (22.39)	20.48 (20.06)	4.72 (1.19)
NCT01313208	Placebo	97	24	19.6	29.9	50.5				8.88 (11.03)	
NCT00445770	Placebo	137	24	29.2	51.1	19.7	3.82 (4.43)	3.73 (3.54)	29.99 (20.33)	9.51 (16.34)	3.37 (1.3)
NCT00160602	Placebo	17	24	11.8	76.5	11.8	9.82 (8.29)	9.76 (6.91)	35.59 (23.34)	27.18 (40.68)	4.66 (1.39)
NCT00152386	Placebo	42	24	14.3	71.4	14.3	6.66 (7.09)	6.28 (6.4)	32.57 (21.94)	16.45 (18.26)	4.08 (1.47)
NCT00717236	Placebo	182	12	4.9	44.5	50.5	9.91 (7.67)	7.53 (6.39)	49.74 (23.91)	18.57 (23.49)	4.82 (1.35)
NCT00548834	Placebo	28	24	7.1	53.6	39.3	7.32 (6.14)	5.68 (4.87)	26.07 (11)	10.42 (10.69)	3.98 (0.98)
NCT00674362	Placebo	67	24	16.4	20.9	62.7	5.35 (5.19)	3.66 (3.45)	34.27 (23.5)	11.82 (14.59)	3.83 (1.12)
NCT01519791	Placebo	211	24	33.6	52.6	13.7	5.03 (6.08)	3.85 (4.57)	26.24 (23.39)	9.82 (17.5)	3.37 (1.4)
NCT00264537	Placebo	144	24	30.6	34.7	34.7	7.8 (7.99)	4.72 (5)	37.42 (25.95)	13.7 (20.12)	4.05 (1.57)
NCT00264550	Placebo	114	24	21.1	43	36	7.28 (7.03)	4.8 (4.74)	39.65 (24.12)	11.76 (13.95)	4.13 (1.26)
NCT00299546	Placebo	112	24	13.4	36.6	50	10.03 (7.52)	7.26 (6.02)	44.79 (27.12)	15.57 (22.8)	4.7 (1.31)
NCT00361335	Placebo	118	24	14.4	39.8	45.8	9.58 (7.45)	7.19 (6.11)	42.6 (24.56)	11.63 (18.47)	4.52 (1.33)
NCT00973479	Placebo	184	24	18.5	44.6	37	6.53 (4.85)	3.96 (3.3)	45.01 (23.25)	13.53 (15.8)	4.18 (1.11)
NCT01248780	Placebo	122	24	19.7	28.7	51.6	6.35 (5.08)	3.7 (3.71)	54.09 (23.48)	15.7 (21.28)	4.19 (1.3)
NCT00269867	Placebo	51	30	7.8	41.2	51	9.92 (8.1)	11.27 (7.21)	45.53 (24.52)	28.24 (38.57)	5.05 (1.31)
NCT00236028	Placebo	230	30	32.6	48.7	18.7	7 (7)	6.17 (5.78)	31.41 (23.52)	9.41 (14.65)	3.95 (1.3)

TJC28 =Tender joint count, SJC28: Swollen joint count; PGA: Patient Global assessment.

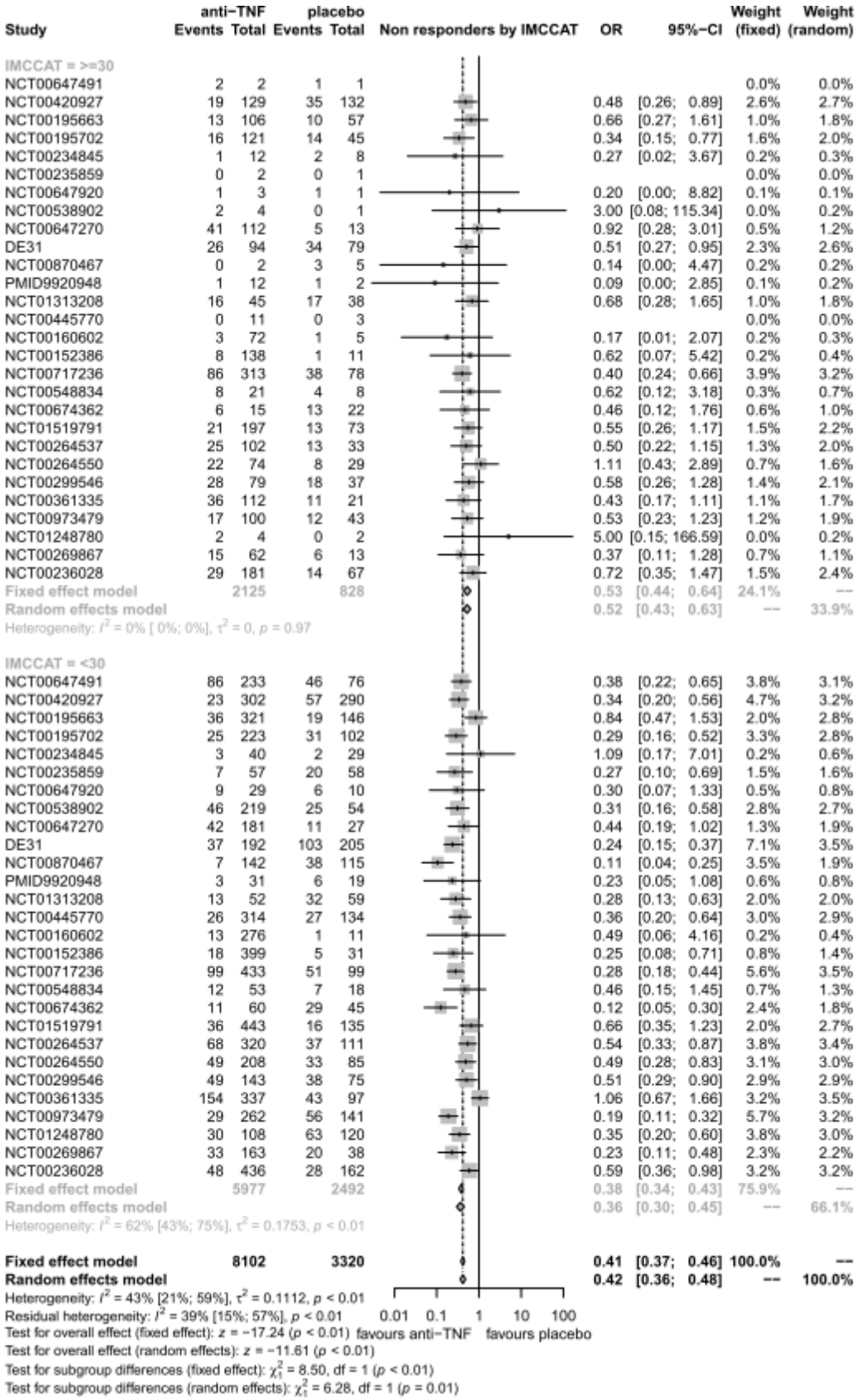
Supplemental document 12: Forest plot - Mean difference ΔDAS28(CRP) between TNF inhibitors versus Placebo by treatment.



Supplemental document 13: Forest plot - Mean difference final DAS28(CRP) between TNF inhibitors versus Placebo by treatment.



Supplemental document 14: Forest plot - EULAR Non-response between TNF inhibitors versus Placebo by obesity.



Supplemental document 15: Sensitivity analysis: p values for subgroup difference for ΔDAS28(CRP), DAS28(CRP) final, good EULAR response and non-EULAR response between TNF inhibitors and placebo without NCT00870467 study

	Number of studies	p-value for subgroup difference			
		ΔDAS28(CRP)	DAS28(CRP) final	Good response	Non-response
Smoking					
Yes	13	0.89	0.87	0.75	0.99
No					
Physical activity					
Yes	5	0.81	0.58	0.87	0.95
No					
Gender					
Women	26	0.31	0.69	0.45	0.97
Men					
Age					
>50	26	**0.08**	0.15	0.57	0.28
<=50					
BMI					
>= 30	27	**0.07**	**0.04**	0.17	**0.02**
< 30					
RF status					
Positive	27	**0.07**	0.18	0.57	0.16
Negative					
ACPA status					
Positive	12	0.42	0.72	0.90	0.41
Negative					
Disease duration					
< 2 years	21	0.28	**0.06**	0.70	0.29
2-10 years					
=>10 years					
Baseline DAS28					
> 5.1	26	0.23	0.39	0.89	0.35
<= 5.1					

ACPA = Anti-citrullinated protein antibodies, Baseline DAS28 = DAS28(CRP) score at baseline, BMI = Body Mass Index, RF= Rheumatoid factors.

Vu, les directeurs de Thèse

Vu, le Doyen

De la Faculté de Médecine de Tours

Tours, le

LAW-WAN Johan

67 pages – 4 tableaux – 4 figures – 15 annexes

Résumé :

INTRODUCTION : La réponse aux anti-TNF dans la polyarthrite rhumatoïde (PR) est hétérogène. L'objectif de cette étude était d'identifier des sous-groupes de patients répondant davantage aux anti-TNF.

METHODE : Les données individuelles patients de 29 essais contrôlés randomisés (ECR) évaluant l'efficacité d'un anti-TNF par rapport à un placebo ou à un traitement de fond conventionnel ont été obtenues. La réponse au traitement a été étudiée dans les sous-groupes d'intérêt suivants : statut tabagique, activité physique, genre, âge, IMC, profil d'auto-anticorps, durée d'évolution, forte activité initiale de la maladie. Le critère de jugement principal de réponse choisi était la différence moyenne du ΔDAS28(CRP) à 3 ou 6 mois. Les critères secondaires étaient la différence moyenne de DAS28(CRP) à 3 ou 6 mois et l'Odds ratio de la réponse EULAR à 3 ou 6 mois. Les données agrégées de ces ECR ont été poolées par la méthode de Mantel-Haenszel en utilisant des modèles à effets aléatoires. Une méta régression linéaire a aussi été réalisée séparément sur 2 plateformes de partage données.

RESULTATS : Les données individuelles de 11617 patients de 29 ECR ont été analysées. A 3 ou 6 mois, un taux de non réponse significativement plus important a été observé chez les patients obèses (OR 0,52 contre 0,36 pour les non-obèses ; p=0,01). Dans un modèle de régression multivarié effectué sur 7457 patients, les patients traités par anti-TNF avaient un DAS28(CRP) final diminué de 0,02 pour chaque année d'évolution de la maladie (p<0,001) et un DAS28(CRP) final diminué de 0,21 pour les patients ayant un DAS28(CRP) initial >=5,1 (p=0,05).

CONCLUSION : Dans la PR, les patients répondant davantage aux anti-TNF sont ceux étant non-obèses, ayant une durée d'évolution de la maladie importante, et une forte activité initiale de la maladie.

Mots clés : polyarthrite rhumatoïde – anti-TNF – réponse au traitement — sous-groupe – données individuelles patients.

Jury :

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