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Effacité de la triple association Méthotrexate Sulfasalazine et Hydroxychloroquine dans la polyarthrite récente ayant une réponse insuffisante au Méthotrexate : Méta-Analyse d'essais contrôlés randomisés

THESE
PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE
DIPLOME D'ETAT

MAZOUYES Arnaud

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Résumé

Objectifs

Évaluer l'efficacité de la triple association de sDMARDs (synthetic Disease Modifying Anti-Rheumatic Drugs) comprenant du méthotrexate, de la sulfasalazine et de l'hydroxychloroquine par rapport à un traitement par biothérapie type Anti-TNF α (bDMARD) dans le traitement de la polyarthrite rhumatoïde précoce.

Méthodes

Une recherche systématique de la littérature a été réalisée en utilisant PubMed, la base de données Cochrane et les résumés présentés lors de réunions scientifiques de rhumatologie jusqu'en Décembre 2013. Les essais contrôlés randomisés comparant l'efficacité et la sécurité des bDMARD à la triple combinaison ont été inclus. Les données récupérées étaient le score de Sharp modifié par Van der Heijde (SHS), le taux de rémission, la réponse ACR (American College of Rheumatology), les événements indésirables. Les différences entre les groupes ont été évaluées par la différence moyenne standardisée (SMD). L'hétérogénéité a été évaluée.

Résultats

Nous avons analysé 1348 articles. Nous avons extrait les données de cinq essais comprenant 1412 patients (648 dans le groupe de triple association et 764 dans le groupe bDMARDs). A un an, la réponse clinique et radiologique étaient en faveur d'un traitement biologique. A deux années, la progression radiologique était moindre dans le groupe bDMARD (SMD = 0,45 IC 95% [0,17, 0,72], $p = 0.001$, $I^2 = 68\%$). La proportion d'effets indésirables graves était similaire dans les deux groupes OR (Odds Ratio) = 1,02 (IC à 95% [0,68,1,52], $p = 0,92$, $I^2 = 0\%$). Les événements indésirables gastro-intestinaux étaient plus élevés dans le groupe de la triple association (OR = 1,75 (IC à 95% [0,73,4,21], $p = 0,21$, $I^2 = 75\%$) mais les événements indésirables infectieux étaient plus fréquents dans le groupe bDMARD (OR = 0,50 (IC à 95% [0,35,0,70], $p < 0,0001$, $I^2 = 36\%$).

Conclusion

Le traitement biologique semble être plus efficace que la combinaison triple en terme de progression radiologique dans la PR avec réponse inadéquate au méthotrexate.

Efficacy of Triple Association Methotrexate, Sulfasalazine and Hydroxychloroquine in early rheumatoid arthritis with insufficient response to Methotrexate: meta-analysis of randomized controlled trials

Objectives

To evaluate the efficacy of the triple synthetic Disease Modifying Anti-Rheumatic Drugs (sDMARD) combination Methotrexate , Sulfasalazine and Hydroxychloroquine versus a biologic DMARD (bDMARD) in the treatment of early rheumatoid arthritis.

Methods

A systematic literature search was performed using the PubMed, and Cochrane database and abstracts presented at rheumatology scientific meetings until December 2013. Randomized controlled trials comparing the efficacy and the safety of biologic DMARD with the triple combination were included. Outcomes measure were Van der Heijde modified Sharp score (SHS), remission rate , ACR criteria response, adverse events. Differences between groups were assessed by standardized mean differences (SMD=difference between groups of mean outcome variation from baseline/Standard Deviation at baseline). Heterogeneity was assessed.

Results

A total of 1378 abstract were screened. We extracted data from 5 trials including 1412 patients (648 in the triple combination group and 764 in the bDMARD group. At year one, clinical and radiological response are in favor of biological treatment. At year 2, there is less radiological progression in the bDMARD group (SMD=0.45 CI 95% [0.17, 0.72], p=0,001, I²=68%). The proportion of serious adverse effects was similar in both groups OR=1.02 (95%CI [0.68,1.52],p=0,92, I²=0%). Gastro-intestinal adverse events were higher in the triple combination group (OR=1,75 (CI 95% [0.73,4,21], p=0,21 ,I²=75%)Infectious adverse events were more frequent in the bDMARD group (OR=0,50 (CI 95% [0.35,0.70], p<0,0001, I²=36%).

Conclusion

Biological treatment seems to be more efficient than triple combination in terms of radiological progression in RA with inadequate response to Methotrexate.

Efficacy of Triple Association Methotrexate, Sulfasalazine and Hydroxychloroquine in early rheumatoid arthritis with insufficient response to Methotrexate: meta-analysis of randomized controlled trials

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Introduction

the current recommendations in early rheumatoid arthritis (RA) focus on achieving clinical remission as soon as possible

The concept of a window of opportunity has emerged in early RA, based on a time frame within there is a higher response to intensive treatment strategies leading to a better chance for sustained low disease activity and remission(1,2).

Methotrexate allows about 30% to 50% of early RA patients to achieve a low disease activity(3,4). Among the several potential DMARDs combinations, the combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ) has been shown to be the most effective(5). In the T-REACH trial(6), the triple combination was superior to a single sDMARD in the early RA with high probability of radiographic progression. O'Dell *et al.*(7) and Calguneri *et al.*(8) also described the long term interest of the triple combination in RA.

During the past few years, several studies comparing the effect of a single sDMARD versus medication triple combination were performed in patients suffering from Rheumatoid Arthritis(7,8). Nevertheless, conclusions of those studies are often contradictory (9), and guidelines for prescribing the triple combination in early RA are still unclear (10,11).

Therefore we performed a systematic literature review to compare the efficacy and the safety of triple combination and bDMARD in early rheumatoid arthritis with insufficient response to MTX.

Methods

We performed a systematic literature search of studies comparing the efficacy and the safety of a triple combination MTX, SSZ and HCQ versus a bDMARD in the treatment of early RA.

Search strategy

An extensive search of Pubmed and Cochrane was made by two reviewers (AM and ACB) concerning articles until December 2013. The following keywords were used for database screening ("Hydroxychloroquine"[Mesh] OR "Methotrexate"[Mesh] OR "Sulfasalazine"[Mesh]) AND ("Arthritis, Rheumatoid"[Mesh] OR "rheumatoid"[tw]). We completed our screening with a second combination: (("Hydroxychloroquine" [Mesh] OR "Methotrexate" [Mesh] OR "Sulfasalazine" [Mesh] OR "Drug Therapy, combination" [Mesh]) AND ("Arthritis,Rheumatoid" [Mesh] OR "rheumatoid" [tw])) NOT (("Hydroxychloroquine" [Mesh] OR "Methotrexate" [Mesh] OR "Sulfasalazine" [Mesh])AND ("Arthritis, Rheumatoid" [Mesh] OR "rheumatoid"[tw])). The only limit of the search was “clinical trial”. Another screening in the Cochrane database with the following keywords was performed: “[Methotrexate] explode all trees OR MeSH descriptor : Hydroxychloroquine] explode all trees OR MeSH descriptor: [Sulfasalazine] explode all trees) AND MeSH descriptor: [Arthritis, Rheumatoid] explode all trees”.

A hand search of references concerning included studies and abstracts presented at Annual Scientific Meetings of the American college of Rheumatology (ACR) the European League against Rheumatism, and the French Society of Rheumatology published in from November 2009 to November 2013 completed the literature search. A search on the ClinicalTrials.gov Web site was also performed to identify randomized studies that were not yet published.

Study selection

Inclusion criteria were (i) randomized controlled trials (RCTs) that included (ii) early (disease duration <24 months) RA patients as defined by the 1987 ACR criteria(12) or the 2010 EULAR/ACR classification(13) with (iii) insufficient response to MTX and (iv) stable doses

of non-steroid anti-inflammatory drugs (NSAIDs) and steroid (less than 10mg/day at least 1 week before the inclusion, treated (v) either by the triple combination and bDMARD (vi) with stable doses of (NSAIDs) and steroids. MTX doses ranged from 10mg/week to 25mg/week, SSZ doses ranged from 1 to 2g/day and HCQ doses were 400mg /day.. Infliximab dose ranged from 3mg/kg to 10mg/kg i.v., etanercept dose was 50 mg/week s.c. and adalimumab 40 mg all 2 weeks s.c..

Outcome measures

We applied the Cochrane Musculoskeletal Group recommendations to select outcome measures (14). We reported ACR70 response (15), Sharp van der Heijde Score (SHS) (16), remission (17). We also reported the number of completers and the adverse effects.

Quality assessment

Two authors (AM and ACB) assessed the methodological quality of each study included in the meta-analysis on the JADAD scale (ranging from 0 to 5), where a high score indicates high quality methodology. When disagreements remained after discussions between both reviewers, a third reviewer (A.B.) was consulted.

Data extraction

Two investigators (AM and ACB) independently selected articles among those screening with keywords previously reported and collected data using a predetermined form including patients characteristics (number, gender, age, Body Mass Index (BMI), disease duration, current and past treatment with sDMARDs or bDMARDs, the use of NSAID or corticoids, rate of rheumatoid factors (RF) or Anti-citrullinated protein antibody (ACPA) positive patients, Health Assessment Questionnaire (HAQ) scale(18), Disease Activity Score in 28 joints (DAS 28)(19), SHS(16), remission rate (ACR/EULAR)(17), ACR criteria response(15), adverse events). Data were collected at several end points: 12 months, 24 months. When a trial was reported in several publications, the more informative publication was included in the meta-analysis. When studies reported more than 2 subgroups, we included only the first intervention group described in this study and its corresponding control group.

Statistical analysis

The efficacy of triple combination was compared to the dDMARD in each study by the calculation of the standardized mean difference (SMD; difference between both groups of mean outcome variation from baseline/SD at baseline) and 95% confidence interval (95% CI). Individual SMDs were pooled using the method of the inverse of variance. Intervention safety was assessed by the odds ratio (OR) and 95% CI. The results of individual trials were pooled by meta-analysis using the Mantel-Haenszel method. Heterogeneity was examined using an extension of the Q statistic, I^2 (and its 95% CI), which was considered to be statistically significant at values >50%). Inter-reviewer reproducibility for study selection, data extraction and methodological quality assessment was calculated. Inter-reviewer reproducibility was considered to be moderate for kappa coefficients ranging from 0.21 to 0.59, good for kappa coefficients ranging from 0.60 and 0.80 and excellent for kappa coefficients >0.80. Number needed to treat/harm (NNT/NNH) was calculated as 1/risk difference. Meta-analyses were performed with Review Manager 5 (Nordic Cochrane Centre, Rigshospitalet, Denmark) and additional statistical analyses were conducted with StatsDirect (StatsDirect, Cheshire, UK).

Heterogeneity analysis

To explore heterogeneity, studies were combined into 2 or 3 subgroups according to the trial design (JADAD ≤ 3 or > 3). Heterogeneity between the subgroups was tested using a chi-square test. Publication bias was assessed using funnel plot analysis, Begg's test, and Egger's test.

Results

Trial flow

The review process is summarized in supplementary **Figure 1**. A total of 1,378 abstracts were identified by searching databases. Of these, 52 full-text articles were analyzed and 7 articles were finally included in this study. Inter-reviewer reliability was good for abstract selection (Kappa=0.89 95%IC [0.84, 0.94] ; 99% agreement, **Figure 1**).

Study characteristics

7 studies were included concerning 5 trials (BeSt(20,21), RACAT(22), SWEFOT(23,24), IMPROVED(25), TEAR(26)). The mean (SD) JADAD score was 4 (0.89). None displayed a score < 3. Patients received infliximab at weeks 0-2-6-8 concerning SWEFOT study. Concerning BeSt studies, therapy adjustments occurred every 3 months. Etanercept was given weekly in the RACAT and TEAR studies. Adalimumab was given every two weeks (**supplementary Figure 1**).

Patients' characteristics

A total of 1412 patients were included in the meta-analysis, 648 in the triple combination group and 764 in the bDMARD group (256 treated with infliximab, 78 with adalimumab and 430 with etanercept). The population was comparable in terms of age, gender, rate of RF positivity. In the RACAT study, the disease duration was longer. Patient characteristics are summarized in **Table 1**.

Efficacy of triple combination

Clinical and radiological result at year one

Three studies reported clinical data (SWEFOT, RACAT, IMPROVED) after one year of treatment. As the clinical outcome measures were heterogeneous, we could not pool the data. Nevertheless, we showed higher ACR70 response (OR=1.79 (95 %IC=[1.17, 2.72], p=0,007, I²=0%)(**Figure 2A**) in patients treated with bDMARRDs. Remission rate was similar in both groups (OR=1.1 (95%IC=[0.89,2.21], p=0.14, I²=0%)(**Figure 2B**).A trend towards a decrease in the radiological progression was shown in favor of bDMARD SMD=0.12 (95%IC=[-0.04,

0.28], $p=0,65$, $I^2=0\%$) (**Figure 2C**)

Clinical and radiological results at year two

Three studies provided clinical data after two years of treatment (SWEFOT, TEAR and BeSt).

For the ACR70 response and remission rate, the results were similar in both groups with an OR=1.44 (95%IC [0.86,2.43], $p=0,17$, $I^2=0\%$)(**figure 3A**) but in term of remission, no difference was observed OR=1,01 (95%IC [0.7,1,45], $p=0,38$), $I^2=0\%$)(**figure 3B**)

Radiological progression was decreased in the bDMARD group with a SMD=0.45 (IC 95% [0.17, 0.72] , $p=0.001$, $I^2=68\%$ (**Figure 3C**).

Safety of the triple combination

Completers' rate was higher in the bDMARD group, OR=1.44 (95%CI [1.07, 1.95], $p=0.02$, $I^2=0\%$), corresponding to a NNT=15.2, 95%CI [8.3, 85.0] (**Figure 6A**). Withdrawals for adverse events was similar in both groups, OR=1.18 (95%CI [0.71, 1.95], $p=0.52$, $I^2=26\%$), (**Figure 6B**). The proportion of serious and gastro-intestinal adverse events were not statistically different in both groups with respectively OR=1.02 (95%CI [0.68, 1.52], $p=0,92$, $I^2=0\%$)(**Figure 7A**) and OR=1.75 (CI95% [0.73, 4.21], $p=0.21$, $I^2=75\%$)(**Figure 7B**), whereas infections were more frequent in the bDMARD group (OR=0.50 (95%CI [0.35, 0.70], $p<0,0001$, $I^2=36\%$), , NNH=18.2 (95%CI [12.1, 35.1] (**Figure 7C**).

Heterogeneity analysis

The analysis does not show heterogeneity according to the JADAD score. There were no publication bias.

Discussion

Our study is the first systematic review of literature comparing the efficacy of the triple combination with a bDMARD in early RA with an inadequate response to methotrexate. Our study showed better clinical and radiological outcomes in patients treated with bDMARDs compared to the triple combination after two years.

Only RCTs focusing on the efficacy of the triple combination and bDMARD in early RA with insufficient response to MTX exercise were considered in this review, creating two groups with similar demographic disease-related parameters and comparable treatments at baseline and providing a strong internal validity. Included studies used in the meta-analysis RCT with a high methodological quality (JADAD>3) allowing us to increase the number of patients who were analyzed.

Although the addition of a bDMARD has demonstrated its efficacy in RA inadequate response to MTX (27), the combination DMARD should not be overlooked. In some situations, this therapeutic option is particularly interesting, especially for a temporary contra-indication of bDMARD or in countries with limited health care resources.

However the present meta-analysis is associated with some potential limitations. First, some of the included studies displayed methodological bias: open label (21,24), modification of primary end points (22,24,28) and per protocol analysis (22). Secondly, we could only compare the efficacy of the triple combination and TNF inhibitors, as data on other bDMARD whose efficacy has been emphasized in the 2013 EULAR recommendations (27), are lacking. Some of the data we generated should be discussed for triple therapy dissemination. Infectious adverse events were frequent in the triple combination group. We also observe a trend towards an increased gastro-intestinal adverse events in the triple combination group. Secondly, the external validity of this meta-analysis might be hampered by inclusion criteria of patients in the RCT. Indeed, we do not have data to evaluate the compliance. The Antirheumatic Therapies in Sweden (ARTIS) registry shows the proportion of patients discontinuing anti-TNF treatment at one year between 23 and 36% with etanercept,

adalimumab and infliximab (29). Data from the National Databank for Rheumatic diseases showed that among 398 patients, approximately 1 in 2 discontinued the triple combination after 12 months of treatment (30).

Some important outcomes were beyond the scope of this study and could not be explored in this meta-analysis. Choi *et al.*(31) showed an important cost of bDMARDs compared to the triple combination to achieve ACR20 and ACR70 response with a higher probability of achieving the goal with biological treatment. In the BeSt study (32,33), further analysis showed a better quality of life in patients treated by a bDMARD with a still higher cost (but offset by higher productivity). Finally, we were not able to compare the efficacy of the triple combination with the step-up strategy of DMARD combinations. We included data from the BeSt study, where DMARDs were added one by one, whereas in other included studies Methotrexate, Sulfasalazine and Hydroxychloroquine were combined at baseline.

In conclusion, bDMARDs seem more efficient than the triple combination in terms of radiological progression in patients with inadequate response to MTX. However bDMARD displayed an increased risk for infection compared to the triple combination. Further studies are needed for the complementation of the triple combination in early RA management.

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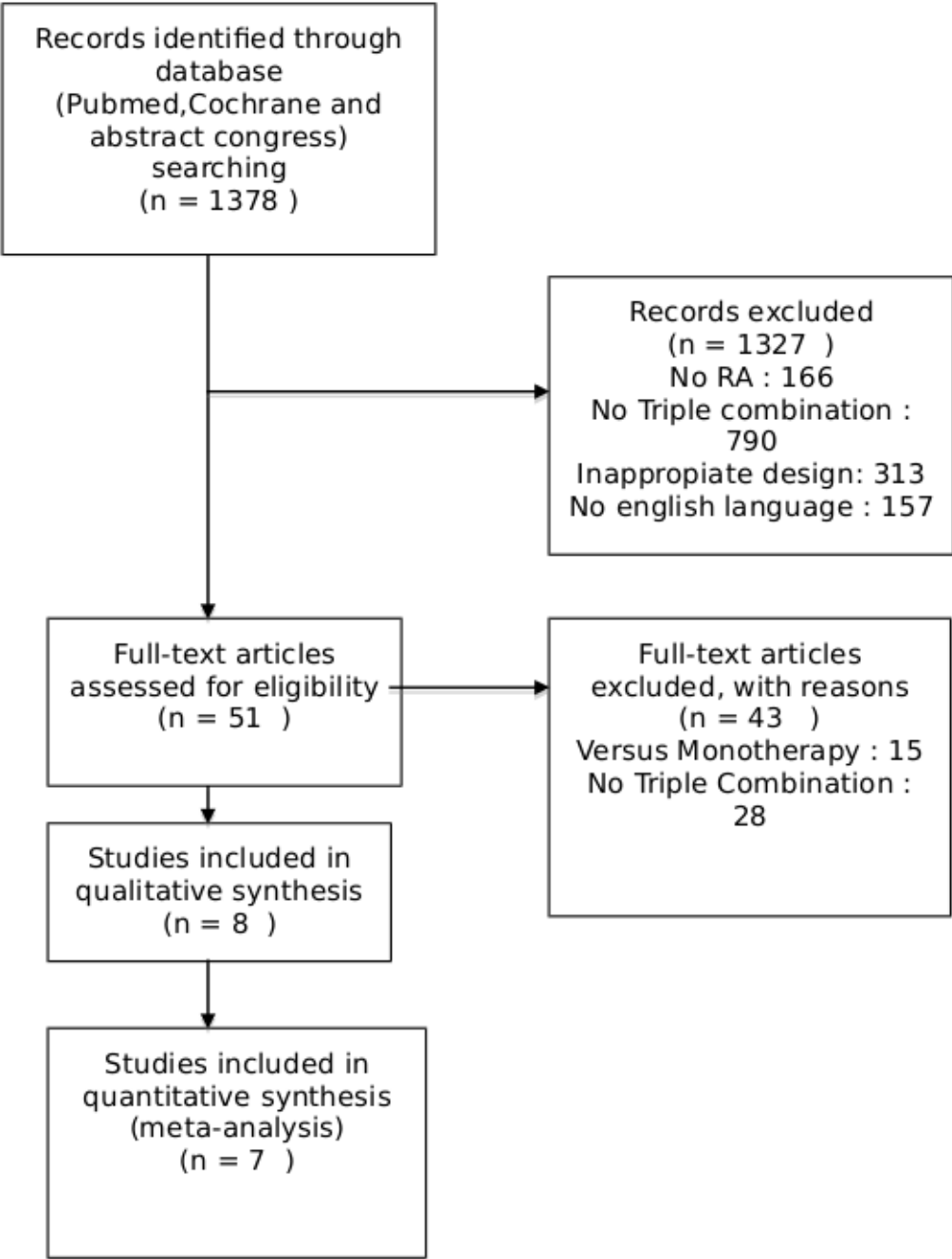
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Figure 1 – Flow Chart



Supplementary figure 1 – Treatment : frequence and dosage

	BeSt	TEAR	SWEFOT	RACAT	IMPROVED
Méthorexate (mg weekly)	15 à 20	20	10 à 25	15 à 25	25
Salazopyrine (mg daily)	2000	2000	2000 à 3000	1000 à 2000	2000
Hydroxychloroquine (mg daily)	400	400 en 2 prises	400	400	
Etanercept		1 injection weekly		1 injection weekly	
Infliximab (mg/kg)	3 à 10 by 8 weeks		3 6 to 8 weeks		
Adalimumab					40 mg by 2 weeks
Corticoids	Allowed by protocol (7,5 mg daily)	Allowed no maximum dose unless DAS < 3,2 max 1 or 2,5/month	No Addition or change in dosage	≤ 10mg daily or NSAIDs	60 daily 7 weeks then 7,5 mg daily
Injection of corticoids	No precision	Once during study	Allowed except during 4 weeks before visit	No precision	No precision

Table 1 - Characteristics of study. JADAD : JADAD Scale, RF : rheumatoid factor, m = months

, w = weeks, y = years, N/A : not available

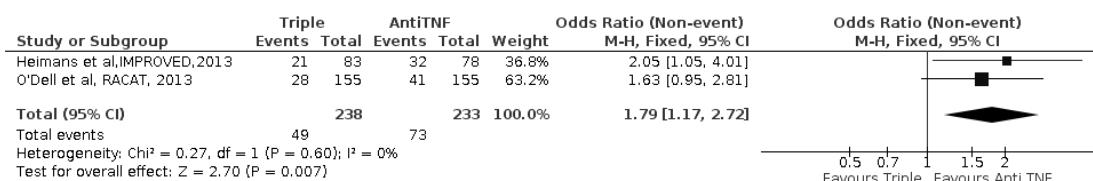
Trial	Triple combination										Anti TNF α									
	JADAD	N	Age (years)	SD	Women(%)	Disease duration	SD or IQR	RF (%)	Erosion (%)	Completers (%)	N	Age (years)	SD	Women(%)	Disease duration	SD or IQR	RF (%)	Erosion (%)	Completers (%)	
BeSe	3	133	54	12	86(71)	26 w	14-56	77(64)	82(70)	N/A	128	54	14	85(66)	23 w	13-46	82(64)	93(73)	N/A	
TEAR	5	124	49,3	12	87(70)	4,5 m	7,6	108(87,1)	N/A	81(65,3)	255	48,6	13	176(69)	2,9 m	5,6	232(91)	N/A	182(71,3)	
SWEFOT	3	130	52,9	13,9	101(78)	6,3 m	3,6	85(65)	N/A	74(56,9)	128	51,1	13,3	79(76)	6,2 m	3,5	88(69)	N/A	90(70)	
RACAT	5	178	57,8	13	77(43,3)	5,5 y	9,3	117(65,7)	N/A	156(87,6)	175	56	13,2	85(48,6)	4,9 y	8	117(66,9)	N/A	145(66,9)	
IMPROVED	4	83	48	14	64(77)	22 w	9-41	41(49)	10(12)	N/A	78	51	14	58(74)	21 w	8-31	43(55)	13(17)	N/A	

Figure 2 – Efficacy of triple combination and Anti TNF α in early rheumatoid arthritis with insufficient response to methotrexate.

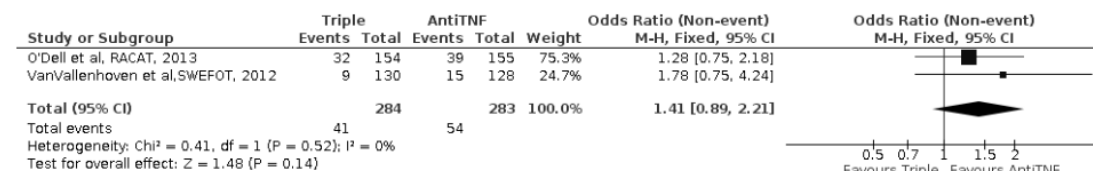
Forrest Plot of ACR70 response(A) and remission rate(B) and Sharp van der Heijde Score (C) at 12 months.

M-H = Mantel-Haenzesl ; 95%IC = 95 % con fiance interval

A.



B



C

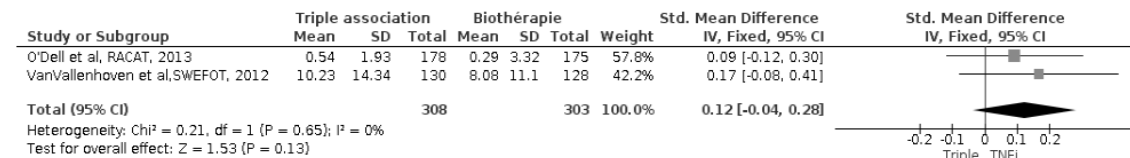


Figure 3 – Efficacy of triple combination and Anti TNF α in early rheumatoid arthritis with insufficient response to methotrexate.

Forrest Plot of ACR70 response(A) and remission rate(B) and Sharp van der Heijde Score (C) at 24 months.

M-H = Mantel-Haenzesl ; 95%IC = 95 % con fiance interval

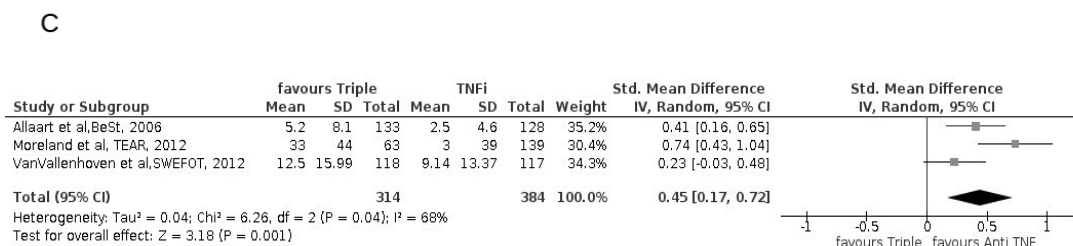
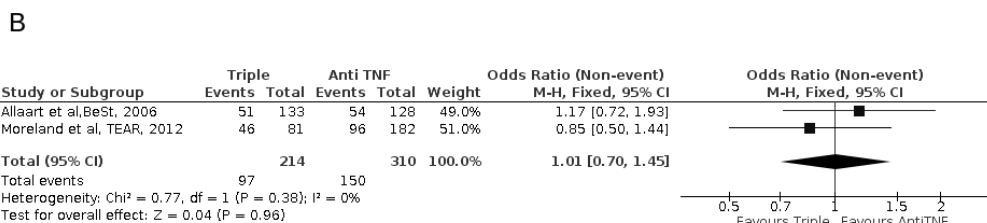
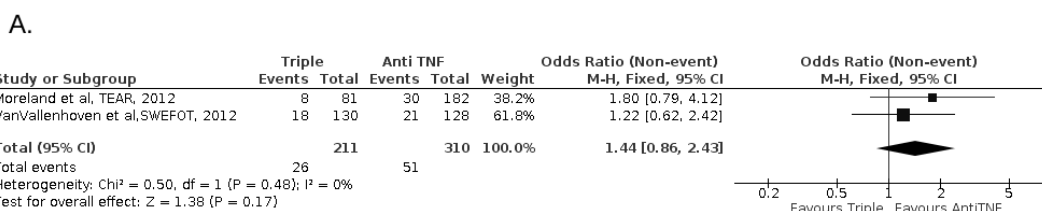
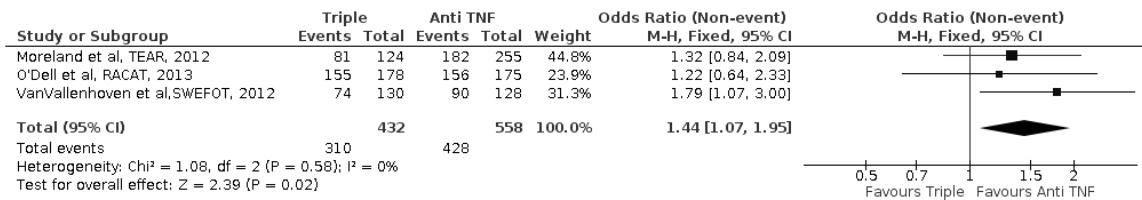


Figure 4 - Efficacy of triple combination and Anti TNF α in early rheumatoid arthritis with insufficient response to methotrexate.

Forrest Plot of ACR criteria for completers (A), withdrawals for adverse effects(B).

M-H = Mantel-Haenzel ; 95%IC = 95 % confidence interval

A.



B

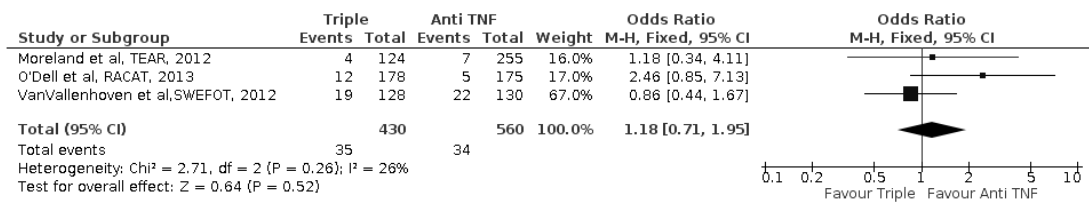
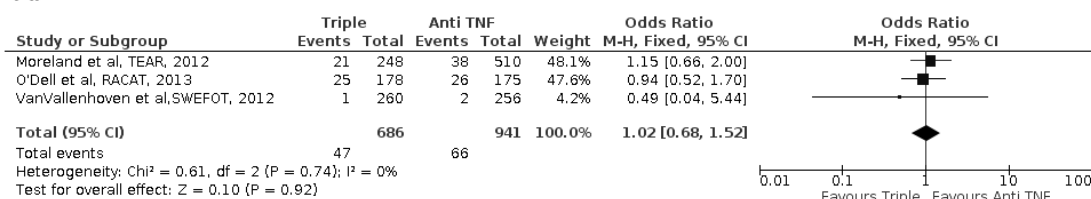


Figure 5 – Efficacy of triple combination and Anti TNF α in early rheumatoid arthritis with insufficient response to methotrexate.

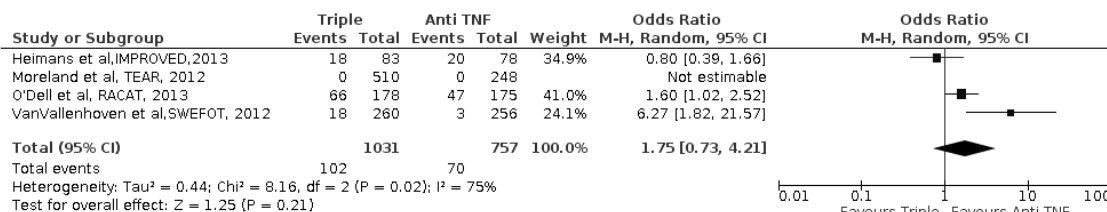
Forrest Plot of serious adverse effects(A), gastro-intestinal adverse effects (B) and infectious adverse event(C).

M-H = Mantel-Haenzesl ; 95%IC = 95 % confiance interval

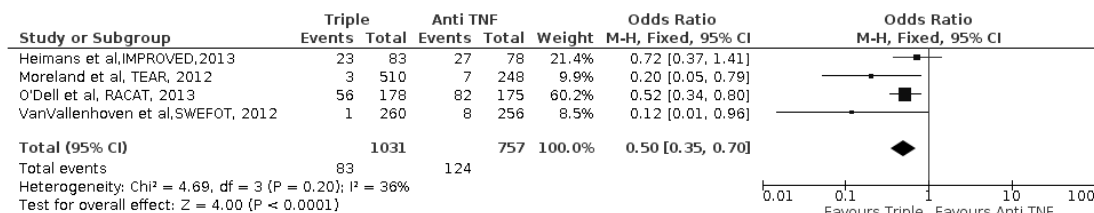
A.

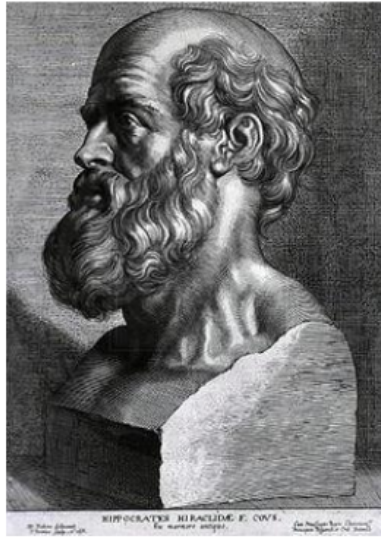


B



C





SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerais mes soins gratuitement à l'indigent et n'exigerais jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

POUR LA CONCLUSION DE VOTRE THESE,

THESE SOUTENUE PAR : MAZOUYES Arnaud

TITRE :

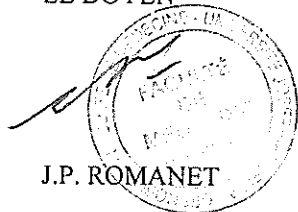
Efficacité de la triple association Méthotrexate Sulfasalazine et Hydroxychloroquine dans la polyarthrite récente ayant une réponse insuffisante au Méthotrexate : Méta-Analyse d'essais contrôlés randomisés

CONCLUSION

In conclusion, bDMARDs seem more efficient than the triple combination in terms of radiological progression in patients with inadequate response to MTX. However bDMARD displayed an increased risk for infection compared to the triple combinaison. Further studies are needed for the complementation of the triple combinaison in early RA management.

VU ET PERMIS D'IMPRIMER
Grenoble, le 22/4/2015

LE DOYEN



J.P. ROMANET

LE PRESIDENT DE LA THESE

PROFESSEUR JUVIN Robert

A handwritten signature in black ink, appearing to be 'R. JUVIN'.