«Μη επιβεβαιούμενος ο κίνδυνος λοιμώξεων από τη συστηματική χρήση κορτικοστεροειδών στη ρευματοειδή αρθρίτιδα»
Dixon WG, et al. Arthritis Res Ther 2011;13:R139

Οι λοιμώξεις είναι μια από τις κυριότερες αιτίες αύξησης της νοσηρότητας και της θνησιμότητας σε ασθενείς με ΡΑ.

Μη επιβεβαιούμενος ο κίνδυνος λοιμώξεων από τη συστηματική χρήση κορτικοστεροειδών στη ρευματοειδή αρθρίτιδα»
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Σκοπός της μελέτης

Συστηματική επανεξέταση και meta-analysis του αποτελέσματος της θεραπείας με γλυκοκορτικοστεροειδή σε σχέση με τον κίνδυνο λοιμώξεων σε ασθενείς με PA

Μέθοδοι

MEDLINE,EMBASE,CINAHL,Cohrane Central Register of Controlled trials database

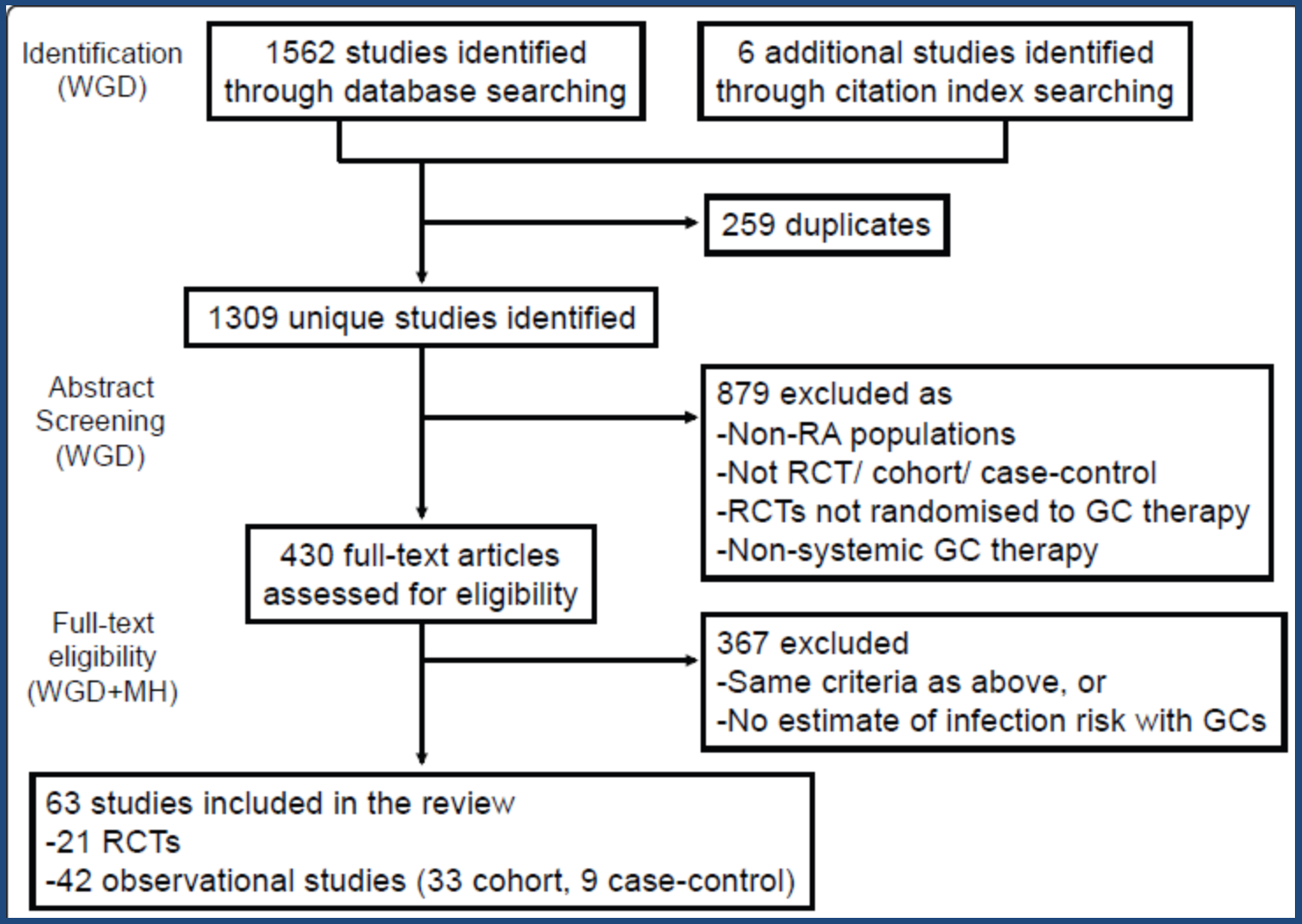
Identification (WGD)
1562 studies identified through database searching
6 additional studies identified through citation index searching
259 duplicates
1309 unique studies identified
Abstract Screening (WGD)
879 excluded as
-Non-RA populations
-Not RCT/ cohort/ case-control
-RCTs not randomised to GC therapy
-Non-systemic GC therapy
430 full-text articles assessed for eligibility
Full-text eligibility (WGD+MH)
367 excluded
-Same criteria as above, or
-No estimate of infection risk with GCs
63 studies included in the review
-21 RCTs
-42 observational studies (33 cohort, 9 case-control)

Table 1 Summary of GC RCTs reporting infection outcomes

First author and year	Country	Setting/Population	Arms of RCT (*n*)	Duration of study	Type of outcome	Result
Boers, 1997 [15]	The Netherlands and Belgium	155 early RA patients from 8 centers	Combination therapy - step-down prednisolone from 60 mg, step-down MTX and SSZ (76) vs SSZ monotherapy (79)	28 weeks	Infections treated as outpatient	12 infections in combination arm, 6 in SSZ monotherapy arm
Chamberlain, 1976 [16]	UK	49 adult RA patients from single center	5 mg prednisolone (20) vs 3 mg prednisolone (10) vs 0 mg prednisolone (19) Allowed concomitant gold	2- 3.5 years	n/a	No infections
Choy, 2005 [17]	UK	91 patients with established RA with incomplete response to DMARDs. Multicenter study	Monthly 120-mg intramuscular depomedrone (48) vs placebo (43) Allowed usual DMARDs	2 years	n/a	No infections either arm
Choy, 2008 [18]	UK	467 patients within 2 years of diagnosis from 42 centers	MTX (117) MTX + cyclosporin (119) MTX + step-down prednisolone (115) MTX + cyclosporin + prednisolone (116)	2 years	a) All-site serious infections b) Respiratory tract infections	a) 7, 3, 4, and 2 serious infections in the four respective arms b) 54, 51, 49, and 55 respiratory tract infections in the four respective arms
Durez, 2007 [19]	Belgium	44 patients with early RA	MTX monotherapy (14) MTX + 1 g iv methylprednisolone[a] (15) MTX + infliximab[a] (15) Infusions weeks 0, 2, 6; then 8 weekly	46 weeks	a) Serious infection b) 'benign' infection	a) No serious infections in any arm b) 14, 12, and 12 benign infections in the three arms, respectively
Durez, 2004 [20]	Belgium	27 patients with active RA despite MTX	MTX + 1 g iv MP week 0 (15) MTX + infliximab weeks 0, 2, and 6 (12)	14 weeks	Serious infections	None in either arm
Gerlag, 2004 [21]	The Netherlands	21 patients with active RA despite DMARDs	60 mg prednisolone week 1, then 40 mg prednisolone week 2 (10) Placebo (11)	2 weeks	n/a	1 skin infection in placebo arm only
Heytman, 1994 [22]	Australia	60 patients with active RA previously treated with NSAIDs	Gold plus either 1 g iv methylprednisolone weeks 0, 4, and 8 (30) or placebo (30)	24 weeks	All patient-reported side effects	No infections reported
Jasani, 1968 [23]	UK	9 patients with erosive RA	4 × 1-week crossover study of ibuprofen 750 mg, aspirin 5 g, prednisolone 15 mg, and lactose as placebo	4 weeks	n/a	No infections reported
Kirwan, 2004 [24]	Belgium, Sweden, UK	143 patients with active RA	Budesonide, 3 mg (37), budesonide, 9 mg (36), prednisolone, 7.5 mg (39), placebo (31)	12 weeks	a) Respiratory infections b) Viral infections	a) 7, 4, 6, and 1 respiratory infections in the 4 groups, respectively. b) 4, 1, 0, and 0 viral infections in the four groups, respectively
Liebling, 1981 [25]	US	10 patients with active RA	Crossover trial of monthly 1-g iv methylprednisolone vs placebo	12 months (6 months per arm)	n/a	4 infections on placebo, 2 on GC
Murthy, 1978 [26]	UK	24 patients with > 30 minutes morning stiffness	Indomethacin, 25 mg × 4 (12), prednisolone, 5 mg (12)	2 weeks	n/a	No infections reported
Sheldon, 2003 [27]	UK	26 patients with active RA	Budesonide (14) or placebo (12) plus usual DMARDs	4 weeks	n/a	2 cases of influenza (one from each group).
Van Everdingen, 2002 [28]	The Netherlands	81 patients with active, previously untreated RA	10-mg prednisolone (40), placebo (41)	2 years	Data reported on infections treated with antibiotics	17 infections in 40 patients in GC arm, 22 infections in 41 patients in placebo arm
Wassenberg, 2005 [29]	Germany/ Austria/ Switzerland	192 patients with active RA, disease duration < 2 years	Gold or MTX plus either 5 mg prednisolone (93) or placebo (96)	2 years	All adverse events collected, reported only if occurred in 3 or more patients	Total 4/93 and 3/96 (Bronchitis in 3/93 prednisolone group, 0/96 placebo group. Influenza in 1/93 prednisolone group, 3/96 placebo)

Table 1 Summary of GC RCTs reporting infection outcomes *(Continued)*

Williams, 1982 [30]	UK	20 patients with active RA	1-g iv methylpredisonolone (10) or placebo (10)	6 weeks	"Serious side effects"	None reported
Wong, 1990 [31]	Australia	40 patients with active RA previously treated with NSAIDs	Gold plus either three pulses of 1 g intravenous methylprednisolone weeks 0, 4, + 8 (20) or placebo (20)	24 weeks	Patients interviewed for all possible side effects	1 injection-site infection in placebo group
Capell, 2004 [32]	UK	167 patients with active RA on no DMARD therapy	SSZ plus either 7 mg prednisolone (84) or placebo (83)	2 years	Withdrawals due to side effects	No discontinuations due to infection in either group
Svensson, 2005 [33]	Sweden	250 patients with active disease on DMARD therapy	DMARD + prednisolone, 7.5 mg (119), DMARD alone, open, no placebo (131)	2 years	Adverse events leading to withdrawal	1 abscess in non-prednisolone group. No infections leading to discontinuation in prednisolone group
Van der Veen, 1993 [34]	The Netherlands	30 patients with active RA	Oral MTX plus either placebo (10) or 100 mg oral prednisolone days 1, 3, and 5 (10) or 1 g iv MP days 1, 3, and 5 (10)	1 year	Adverse events leading to discontinuation of *MTX*	1 pneumonia in placebo group (at week 12)
van Schaardenburg, 1995 [35]	The Netherlands	56 patients with active RA aged > 60 previously treated with NSAIDs	Chloroquine, 100 mg/day (28) (rescue with gold, then SSZ allowed) vs prednisolone 15 mg/day, tapered after 1 month (28)	2 years	Withdrawal due to adverse advents	No discontinuations due to infections in either group

DMARD, disease-modifying antirheumatic drug; iv, intravenous; ivMP, intravenous methylprednisolone; MTX, methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SSZ, sulfasalazine. [a]Infusions weeks 0, 2, 6; then 8 weekly.

Αποτελέσματα

RCTs

- Η θεραπεία με GC δε σχετίζεται με αύξηση του κινδύνου λοίμωξης.(RR:0,97)
- Μικρός αριθμός περιστατικών δείχνει ότι δε μπορεί να αποκλειστεί κλινικά σημαντική αύξηση ή μείωση του κινδύνου.

Μελέτες παρατήρησης

- RR:1,67
- Σημαντική ετερογένεια
- Δοσοεξαρτώμενο αποτέλεσμα.

Συμπεράσματα

- Ασυνεπείς αναφορές ασφάλειας στις RCTs.
- Μεγάλη ετερογένεια και προκατάληψη(bias) δημοσιεύσεων στις μελέτες παρατήρησης.
- Δεν υπάρχει τελικό συμπέρασμα!

- Οι γιατροί πρέπει να επαγρυπνούν για επεισόδια λοίμωξης σε ασθενείς με PA και θεραπεία με GC!