Associazione Neurologia Emergenza Urgenza

ANEU
III National Conference
8 -10 March 2018, Bologna

Oral versus intravenous steroids for Multiple Sclerosis relapse

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Multiple Sclerosis Relapse Treatment

Glucocorticoids are recommended as the standard of care for acute Multiple Sclerosis (MS) relapses, since their proven effectiveness to reduce the severity of clinical impairment and hasten the recovery

Notwithstanding …

- A **standard protocol** has **not been established**
- High **variability** in therapeutic regimens prescribed in clinical practice still exists
- One question to be definitively addressed is the most desirable route of drug administration
  - intravenous (iv) methylprednisolone is often the first choice, although its administration is cumbersome
  - oral preparations could offer many advantages

One Main Question is …

Do differences exist in the treatment efficacy, safety and tolerability between iv and oral steroids?

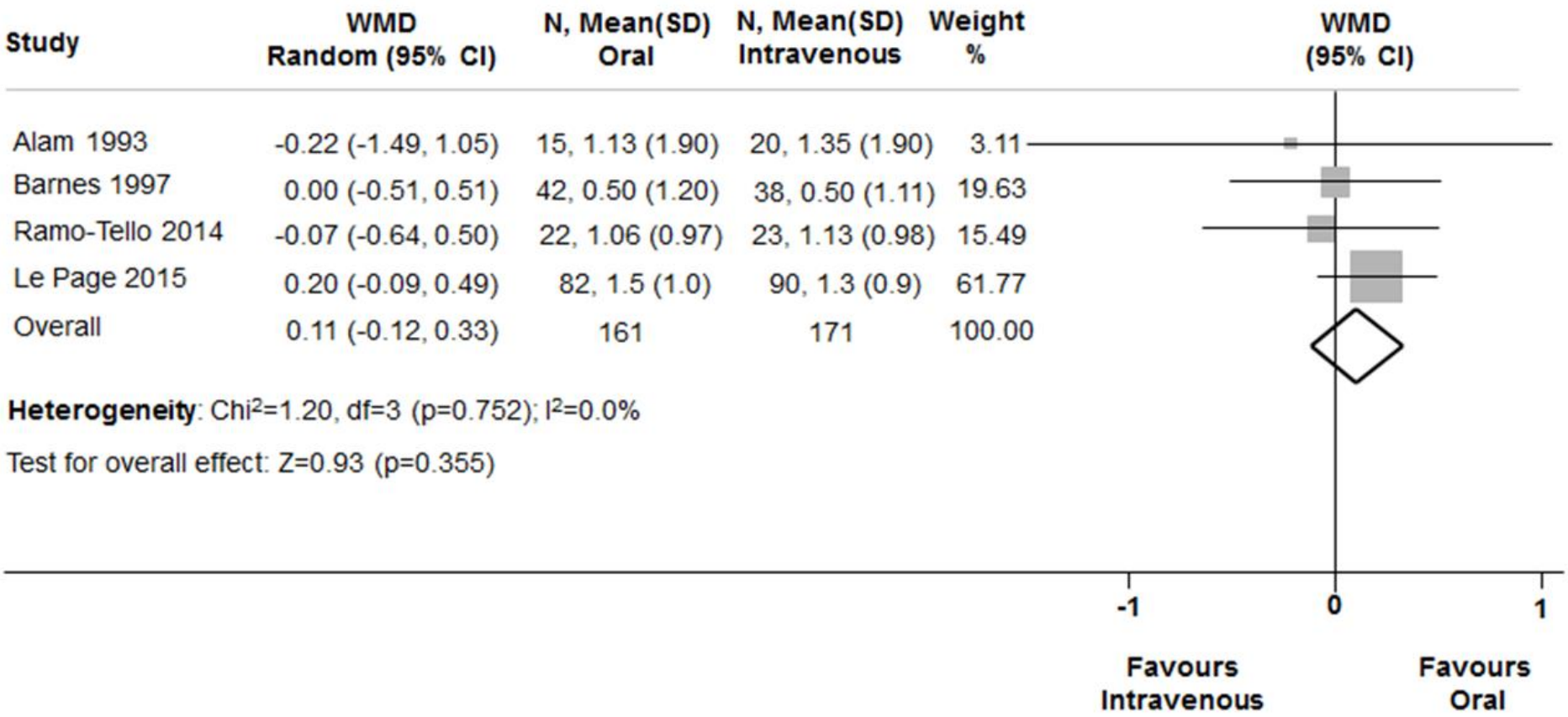
Looking at the evidence

- **Six randomized**, parallel group **trials** with direct comparison between oral and iv steroid treatments
- A total of **419** participants,

210 for oral and 209 for iv groups

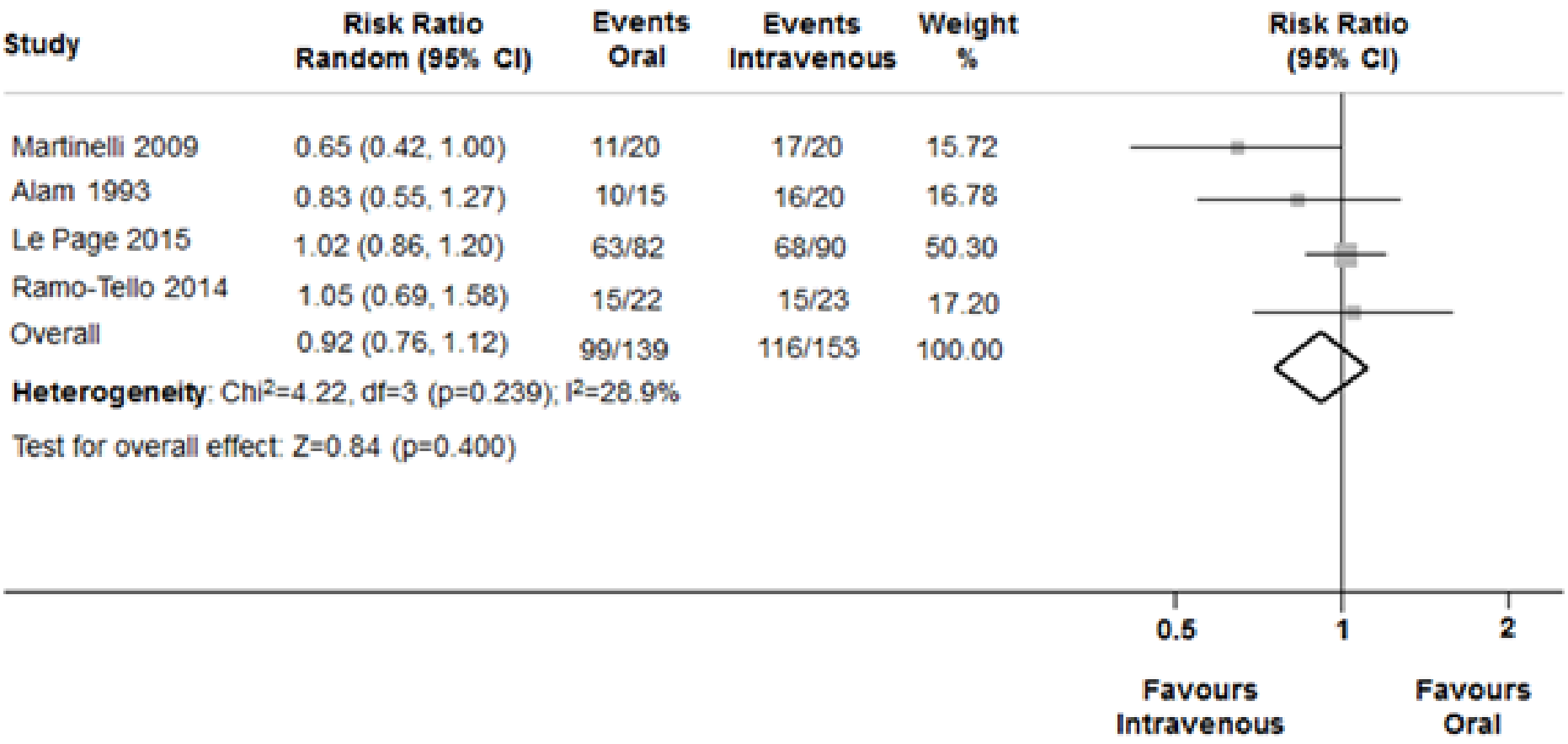
Clinical recovery at 4 weeks

- Mean reduction of EDSS score



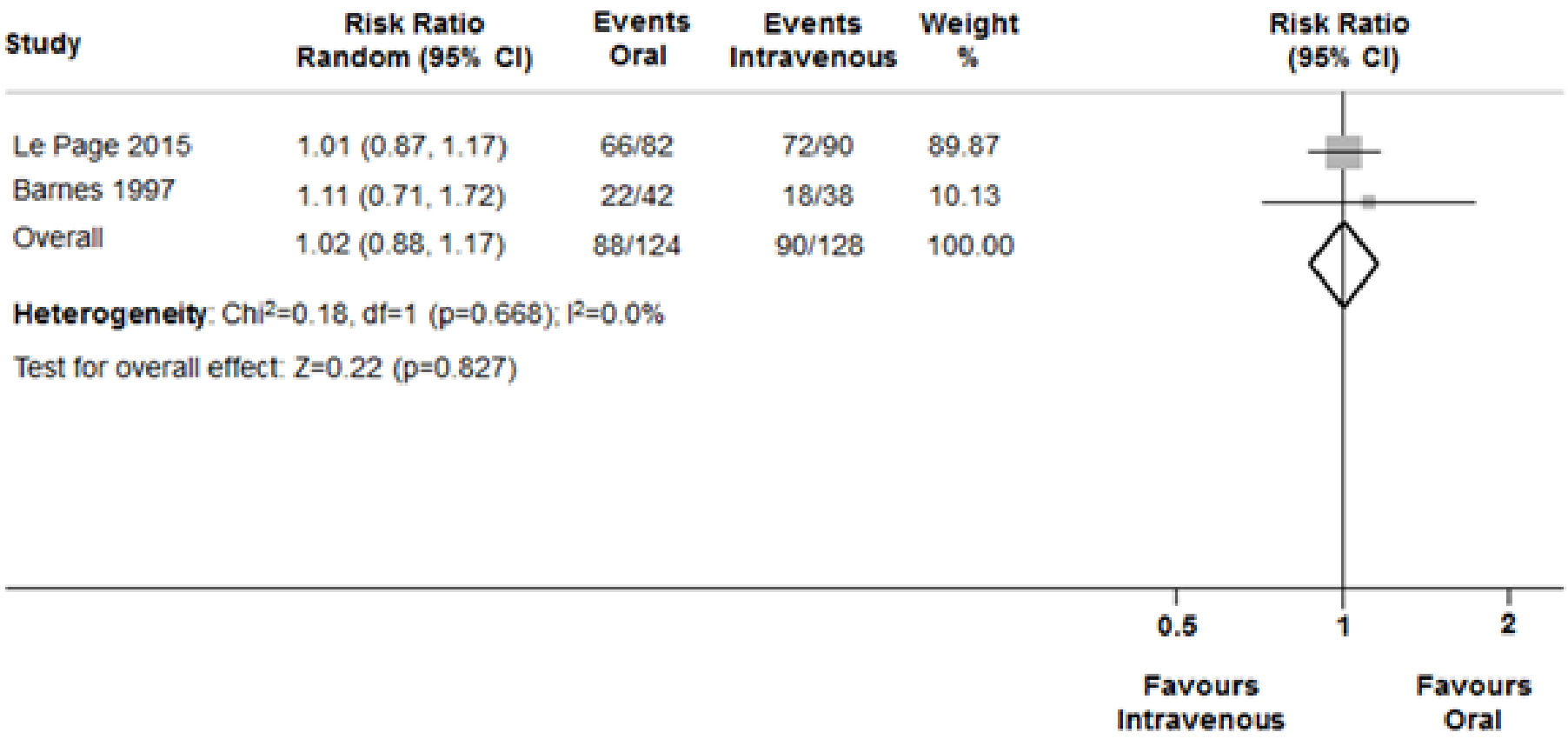
Clinical recovery at 4 weeks

- Improvement by at least one EDSS point



Clinical recovery at 4 weeks

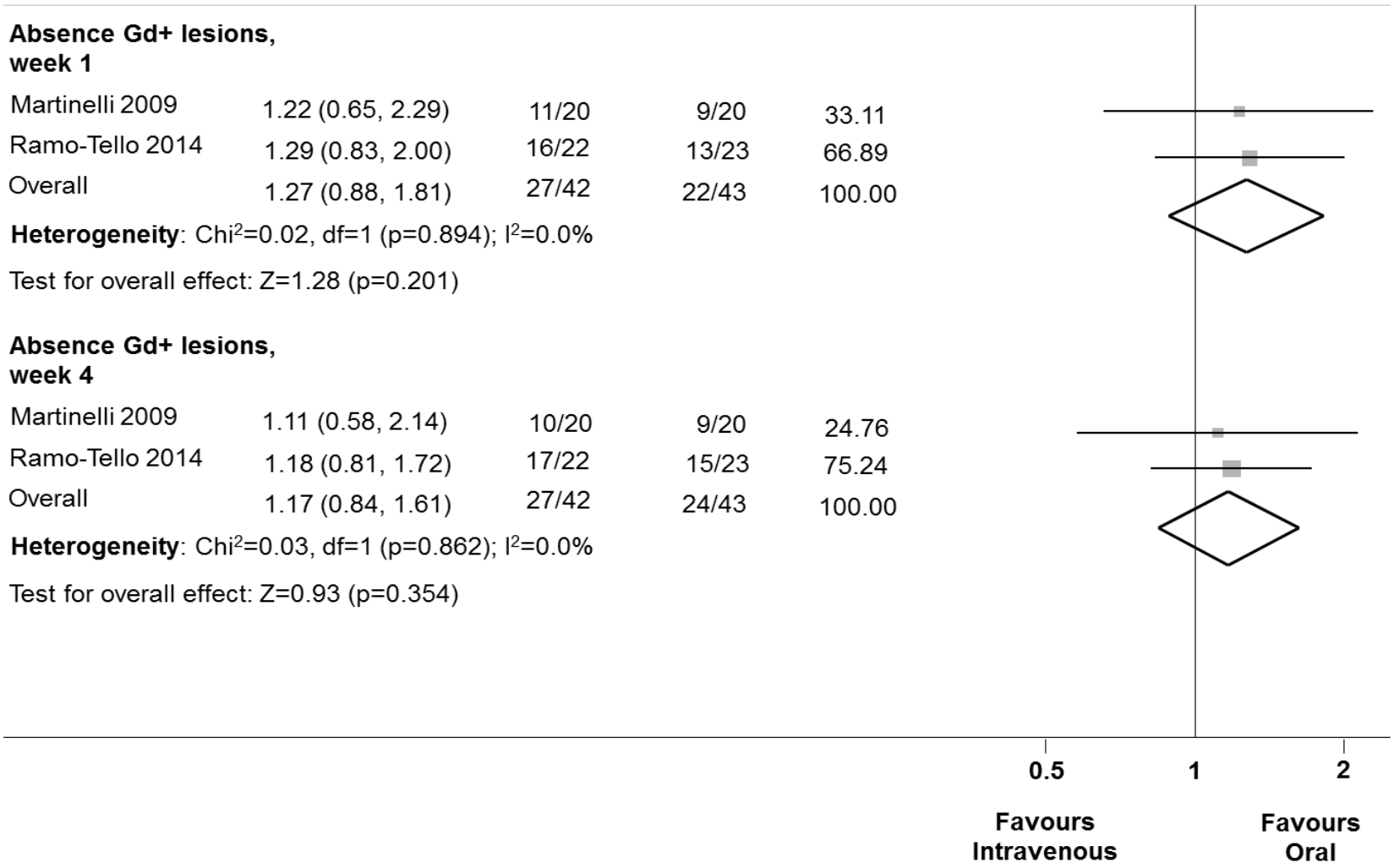
- Improvement of the most affected functional system by at least one EDSS point



Radiological response (weeks: I and 4)

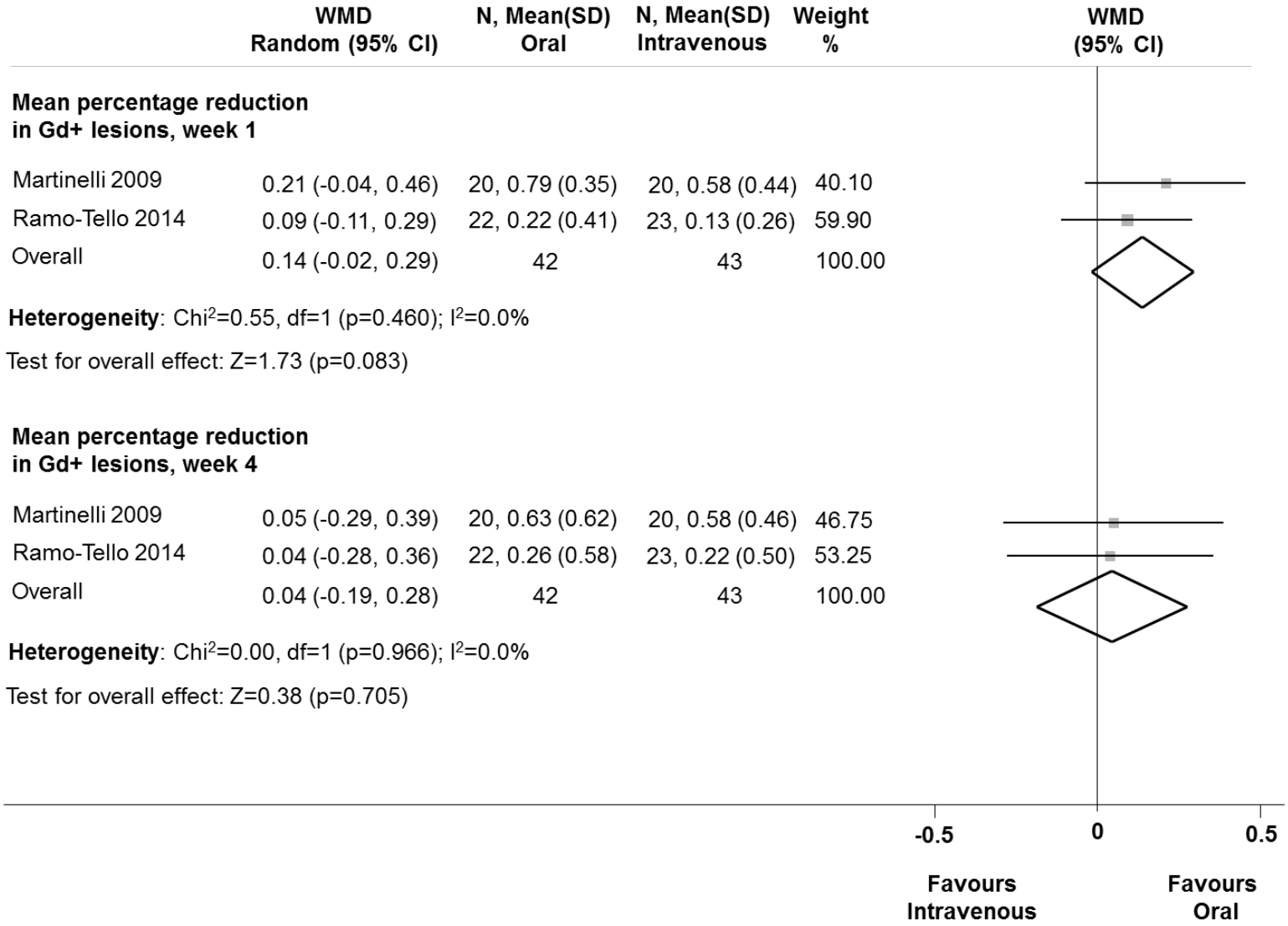
- Absence of Gd-enhancing lesions

Study or subgroup	Risk Ratio Random (95% CI)	Events Oral	Events Intravenous	Weight %
Absence Gd+ lesions, week 1				
Martinelli 2009	1.22 (0.65, 2.29)	11/20	9/20	33.11
Ramo-Tello 2014	1.29 (0.83, 2.00)	16/22	13/23	66.89
Overall	1.27 (0.88, 1.81)	27/42	22/43	100.00
Heterogeneity: Chi^2=0.02, df=1 (p=0.894); I^2=0.0%				
Test for overall effect: Z=1.28 (p=0.201)				
Absence Gd+ lesions, week 4				
Martinelli 2009	1.11 (0.58, 2.14)	10/20	9/20	24.76
Ramo-Tello 2014	1.18 (0.81, 1.72)	17/22	15/23	75.24
Overall	1.17 (0.84, 1.61)	27/42	24/43	100.00
Heterogeneity: Chi^2=0.03, df=1 (p=0.862); I^2=0.0%				
Test for overall effect: Z=0.93 (p=0.354)				



Radiological response (weeks: 1 and 4)

- Mean % reduction in Gd-enhancing lesions count



Adverse Events

Side effect	Number of studies	Participants (oral/IV)	Risk ratio (M–H, random, 95% CI)	*p* value
Gastric pyrosis	3	145/143	1.02 (0.77–1.35)	0.882
Cutaneous rash	3	145/143	1.06 (0.60–1.89)	0.832
Anxiety	3	145/143	1.07 (0.79–1.45)	0.680
Insomnia	3	145/143	1.25 (1.07–1.46)	0.005
Dysgeusia	3	145/143	1.07 (0.76–1.51)	0.684
Nausea	2	125/123	0.91 (0.64–1.32)	0.630
Diarrhea	2	125/123	1.31 (0.76–2.26)	0.329
Euphoria	2	125/123	1.28 (0.39–4.15)	0.686
Headache	2	125/123	1.16 (0.97–1.39)	0.098
Palpitations	2	125/123	1.30 (0.90–1.88)	0.170
Vomiting	1	100/99	1.16 (0.56–2.37)	0.695
Hot flashes	1	100/99	1.08 (0.86–1.35)	0.524
Agitation	1	100/99	1.43 (0.98–2.10)	0.065
Depressed mood	1	25/24	2.88 (0.64–12.90)	0.167
Fatigue	1	25/24	0.72 (0.18–2.89)	0.643
Edema	1	25/24	0.64 (0.12–3.50)	0.607
Hypertension	1	20/20	2.00 (0.20–20.33)	0.558
Hypertrichosis	1	20/20	0.50 (0.05–5.08)	0.558
Hyperglycemia	1	20/20	0.33 (0.01–7.72)	0.493
Hiccup	1	20/20	3.00 (0.13–69.52)	0.493
Any AE	2	120/119	1.12 (0.70–1.78)	0.638
Withdrawal due to AEs	2	45/44	2.94 (0.32–27.25)	0.342

Efficacy

- There were **no** meaningful **differences** in both clinical and radiological efficacy outcomes for oral versus iv administration of steroids

- The difference in the average time to total recovery between the two treatment ways was not meaningful

Safety - Tolerability

- The safety and tolerability profiles of oral and iv steroids were quite **similar**
- The meaningful difference emerged in the rate of **insomnia**, which was more common among the orally treated patients, and suggested to preferentially give the drug in the morning and consider symptomatic hypnotics
- Conversely, no excess of gastrointestinal symptoms was associated with oral administration

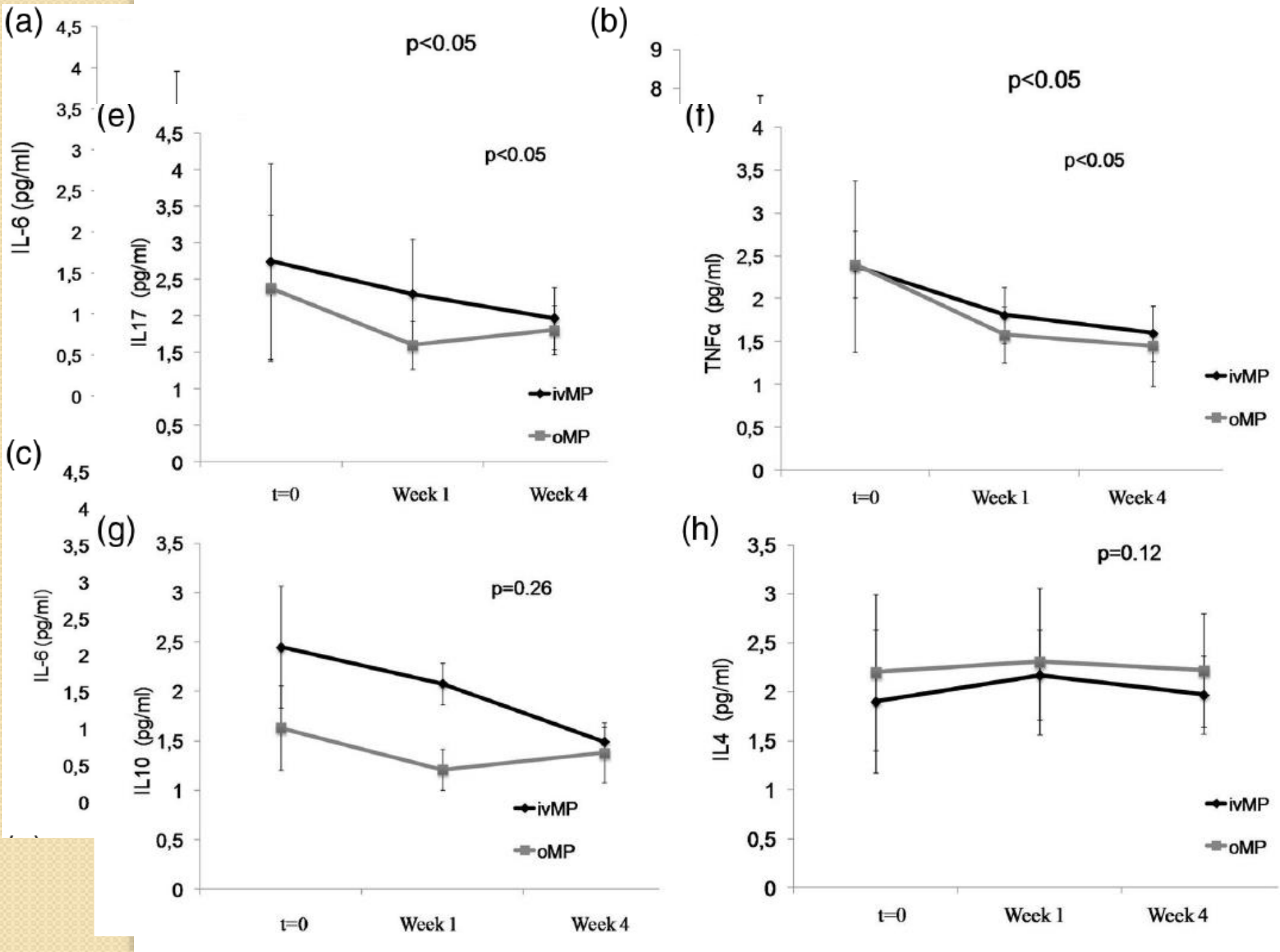
MULTIPLE SCLEROSIS JOURNAL | MSJ

Short Report

Similar biological effect of high-dose oral versus intravenous methylprednisolone in multiple sclerosis relapses

- Grau-Lopez et al. have evaluated the cytokines milieu in MS patients with acute attacks undergoing steroid treatment, and provided immunological evidence that **bioequivalent high dose of oral and intravenous methylprednisolone** is not mechanistically different

Mult Scler 2015;21:646-650


(a)
IL-6 (pg/ml)
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
p<0.05
(b)
9
8
p<0.05
(e)
IL17 (pg/ml)
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
p<0.05
ivMP
oMP
t=0
Week 1
Week 4
(f)
TNFα (pg/ml)
4
3,5
3
2,5
2
1,5
1
0,5
0
p<0.05
ivMP
oMP
t=0
Week 1
Week 4
(c)
IL-6 (pg/ml)
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
(g)
IL10 (pg/ml)
3,5
3
2,5
2
1,5
1
0,5
0
p=0.26
ivMP
oMP
t=0
Week 1
Week 4
(h)
IL4 (pg/ml)
3,5
3
2,5
2
1,5
1
0,5
0
p=0.12
ivMP
oMP
t=0
Week 1
Week 4

Conclusions _ I

- One main challenge in the MS management is **reducing expenses** while **enhancing quality of care**

- **Oral** steroid treatment may
  - contain the **expenses** related to intravenous infusions, hospital stay, and home-care services
  - reduce the lost work productivity and **indirect costs**
  - minimize the **patient discomfort**
  - guarantee a more **rapid** and **easier** access to therapy
  - offer many advantages for both healthcare system and patients

Conclusions _ II

- The **steroid over-use** is one possible risk linked to the oral regimen that could be managed by matching treatment with specialist's evaluation

- The current unavailability of **pre-packaged high-dose oral preparations** represents a logistic limitation that should be promptly addressed

Reading Suggestions

REVIEW

Oral and intravenous steroids for multiple sclerosis relapse: a systematic review and meta-analysis

Simona Lattanzi[1] · Claudia Cagnetti[1] · Maura Danni[1] · Leandro Provinciali[1] · Mauro Silvestrini[1]

J Neurol. 2017;264:1697-1704

RESEARCH ARTICLE

Oral versus intravenous methylprednisolone for the treatment of multiple sclerosis relapses: A meta-analysis of randomized controlled trials

PLoS One. 2017;12:e0188644

Shuo Liu[1,2], Xiaoqiang Liu[1], Shuying Chen[1], Yingxiu Xiao[1], Weiduan Zhuang[1]*

References	Country	Relapse criteria	Time to onset	Treatment arms
Alam et al. [11]	Single-center UK	Symptomatic neurological deterioration of sufficient severity to require steroid treatment and without improvement at the time of study entry	≤4 weeks	OMP 500 mg/day +iv placebo for 5 days IVMP 500 mg/day + oral placebo for 5 days
Barnes et al. [12]	Multicenter UK	Symptomatic neurological deterioration of sufficient severity to justify steroid treatment	≤4 weeks	OMP: 48 mg/day × 7 days, then 24 mg/day × 7 days, then 12 mg/day × 7 days + iv placebo IVMP: 1 g/day + oral placebo for 3 days
Morrow et al. [13]	Single-center Canada	Symptomatic neurological deterioration of sufficient severity to justify steroid treatment	NA	Oral prednisone 1250 mg/day IVMP 1 g/day
Martinelli et al. [14]	Single-center Italy	Clinical attack with documented clinical worsening of ≥1.0 point on the EDSS or a worsening of ≥2.0 points in one of the EDSS FSS, with no improvement at the time of study entry, and ≥1 Gd-enhancing lesion on brain MRI performed within 24 h from neurologic evaluation and before treatment	≤2 weeks	OMP 500 mg × 2/day + sucralfate 2 g × 3/day for 5 days IVMP 1 g/day + sucralfate 2 g × 3/day for 5 days
Ramo-Tello et al. [15]	Multicenter Spain	Moderate (increase 1–2.5 EDSS points) or severe (increase ≥3 EDSS points) clinical attack without improvement at the time of study entry	≤2 weeks	OMP 1250 mg/day + iv placebo for 3 days IVMP 1000 mg/day + oral placebo for 3 days
Le Page et al. [16]	Multicenter France	Clinical attack with documented clinical worsening of ≥1.0 point in one or more scores on the Kurtzke FSS, and resulting in a score ≥2 on the most affected scale (≥3 on the sensory scale)	≤2 weeks	OMP 1000 mg/day + iv placebo for 3 days IVMP 1 g/day + oral placebo for 3 days Retreatment for 2 additional days allowed

Reference Study (year)	Study Arm	Subjects (no.)	Male (%)	Age (years)	Disease Duration (years)	MS course	EDSS Score at Study Entry
Alam et al. (1993) [11]	Oral	15	26.7	41.3 (13.6)	3.8 (3.5)	NA	4.80 (1.90)
	IV	20	20.0	41.6 (12.8)	6.5 (7.4)		4.85 (1.90)
Barnes et al. (1997) [12]	Oral	42	42.9	38.0 (9.6)	6.6 (3.1-10.9)	NA	5.0 (3.5-6.5)
	IV	38	28.9	37.0 (11.1)	6.3 (3.6-13.6)		6.0 (3.5-7.5)
Morrow et al. (2004) [13]	Oral	8	25.0	39 (range 24-61)	5.7 (range 0.6-38)	RR (87.5%)	4.0 (2.0-6.5)
	IV	8					
Martinelli et al. (2009) [14]	Oral	20	31.6	36.0 (8.0)	9.8 (6.3)	RR	3.5 (2.0-5.5)
	IV	20	30.0	31.0 (7.0)	7.2 (6.0)		3.0 (2.0-6.0)
Ramo-Tello et al. (2014) [15]	Oral	25	23.0	39.5 (7.9)	-	RR	3.0 (2.5-4.0)
	IV	24	17.0	37.7 (7.8)	-		4.0 (2.5-4.5)
Le Page et al. (2015) [16]	Oral	100	26.0	35.0 (18.2-62.6)	6.2 (3.4-11.9)	RR	3.5 (3.0-4.0)
	IV	99	25.3	34.7 (18.3-58.7)	5.7 (3.0-10.7)		3.5 (3.0-4.0)

Data are mean (SD) or median (IQR), unless otherwise stated

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Thanks for your attention

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