Best paper in: Tuberculosis

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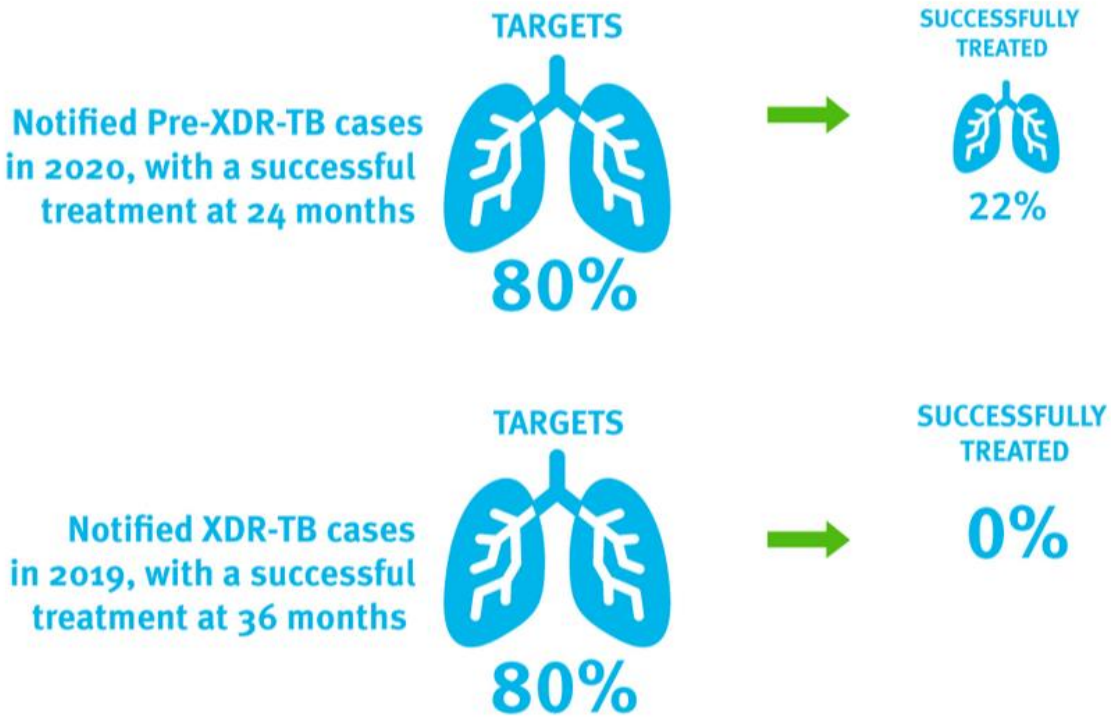
Tuberculosis

La tubercolosi è una delle principali cause di morte da malattia infettiva a livello mondiale.

L'OMS ha lanciato la campagna ''End TB'' con l'obiettivo di ridurre l'incidenza di TB del 80% e di mortalità di quest'ultima del 90%.

Limiti:

- Assenza di un vaccino efficace.
- Test diagnostici;
- Durate dei trattamenti;



Key advances in vaccine development

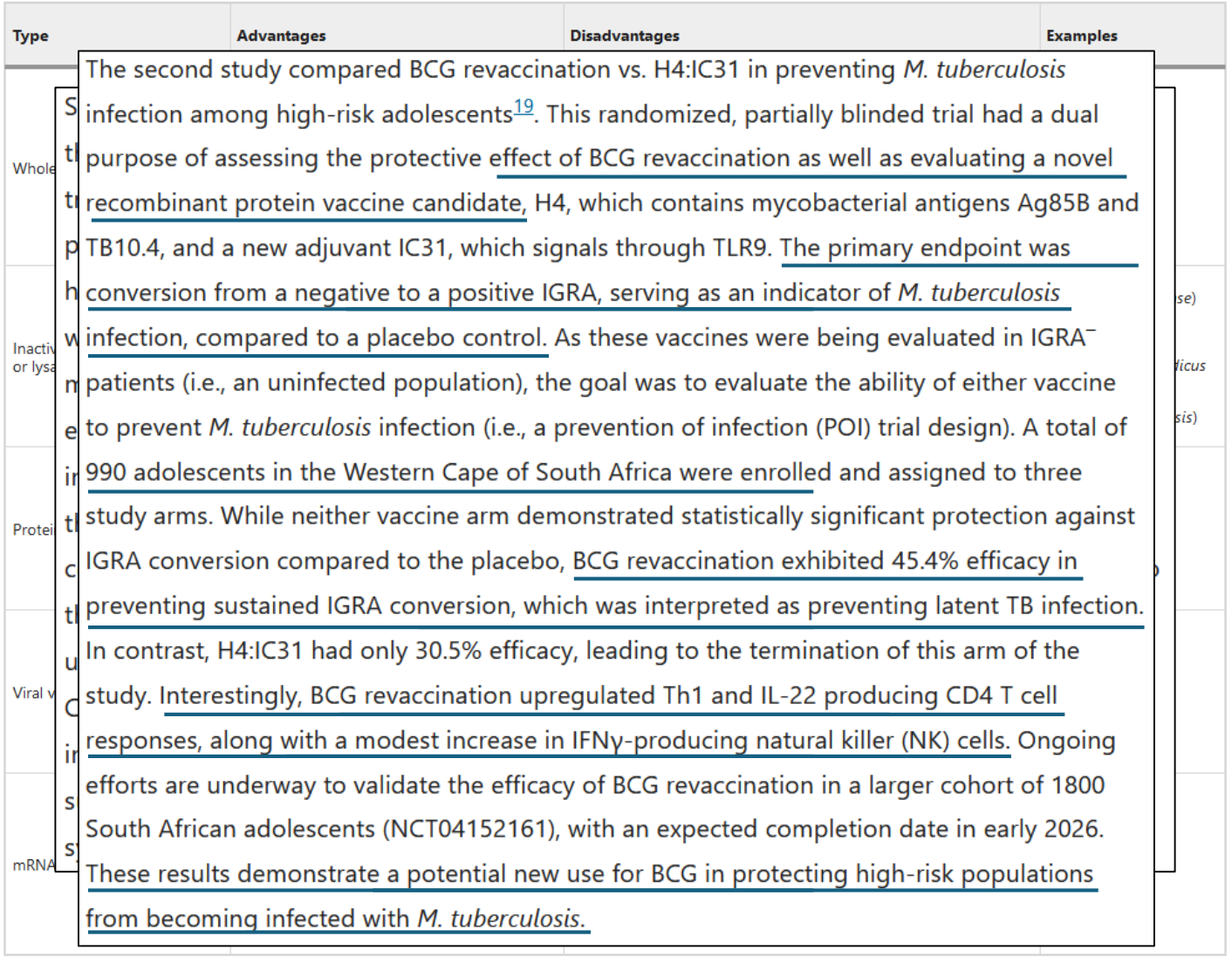
Type	Advantages	Disadvantages	Examples
Whole cell live vaccines	• Generally safe • Generally given as a single dose • Broad range of antigens • Trigger diverse immune responses • Mimic immunity elicited by *M. tuberculosis*	• Not advised for immunocompromised persons	BCG revaccination Intravenous BCG MTBVAC (*M. tuberculosis*) VPM1002 (BCG)
Inactivated whole cell vaccines or lysates	• Safe for immunocompromised persons • Contain diverse repertoire of antigens • Can be used as a prophylactic and post-exposure vaccine	• No immunity to antigens produced during live infection • Generally requires boosting	DAR901 (*M. obuense*) V7 (*M. vaccae*) Immunovac (*M. indicus pranii*) RUTI (*M. tuberculosis*)
Protein subunit and adjuvant	• Safe for immunocompromised persons • Trigger CD4 T cell and antibody responses	• Immune responses are generated to a limited number of antigens • CD8 T cell responses are not elicited • Requires boosting • Requires an adjuvant	AEC/BC02 GamTBvac ID93/GLA-SE M72/AS01E
Viral vectored vaccines	• Generally safe • Trigger robust immune responses • Stimulate CD4, CD8, and antibody responses • Do not require adjuvant	• Strong immune responses to the viral component limit their repeated use • Preexisting immunity against the viral vector limits the use of some vectors	MVA85A AdAg85A RhCMV/TB
mRNA vaccine	• Safe for immunocompromised persons • Speed and flexibility of production • Can elicit different types of immune responses • No pre-existing immunity components	• Like subunit vaccines, immune responses are generated to a limited number of antigens • Relatively untested in the TB field.	ID91

Key advances in vaccine development

Type	Advantages	Disadvantages	Examples
Whole			
Inactiv or lysa			se) ficus sis)
Protei			
Viral v			
mRNA	• Can elicit different types of immune responses • No pre-existing immunity components	• Relatively untested in the TB field.	

Since the MVA85A trial, significant advancements include the results from two recent studies that have re-galvanized the field. First, the M72/AS01E vaccine was evaluated in a Phase 2b trial to prevent disease in a cohort of 3575 HIV-negative adults with latent TB infection (i.e., people who have immunological evidence of *M. tuberculosis* infection but currently do not have clinical symptoms of TB). In this prevention of disease (POD) trial design, participants were randomly assigned to receive either two doses of M72/AS01E or placebo, with a one-month interval between doses. The participants were followed for three years, and the primary endpoint was microbiologically confirmed active, pulmonary TB without evidence of HIV infection[18]. The primary analysis, conducted two years after the second vaccination, revealed that there were 49.7% fewer cases of active TB among persons vaccinated with M72/AS01E compared to the placebo. All individuals in the M72/AS01E cohort developed IgG responses to the M72 protein by the second month after vaccination, and these responses were sustained up to month 36. Furthermore, 23.5% of the M72/AS01E recipients developed polyfunctional CD4 T cells responses that produced IFNγ, TNF, or IL-2 after the first vaccination, which increased to 53.7% by month 36. These results are exciting as this is the first indication that a subunit vaccine can protect *M. tuberculosis*-infected individuals from progressing to active symptomatic TB.

Key advances in vaccine development



Type	Advantages	Disadvantages	Examples
Whole			
Inactiv or lysa			
Protei			
Viral v			
mRNA			

The second study compared BCG revaccination vs. H4:IC31 in preventing *M. tuberculosis* infection among high-risk adolescents[19]. This randomized, partially blinded trial had a dual purpose of assessing the protective effect of BCG revaccination as well as evaluating a novel recombinant protein vaccine candidate, H4, which contains mycobacterial antigens Ag85B and TB10.4, and a new adjuvant IC31, which signals through TLR9. The primary endpoint was conversion from a negative to a positive IGRA, serving as an indicator of *M. tuberculosis* infection, compared to a placebo control. As these vaccines were being evaluated in IGRA$^-$ patients (i.e., an uninfected population), the goal was to evaluate the ability of either vaccine to prevent *M. tuberculosis* infection (i.e., a prevention of infection (POI) trial design). A total of 990 adolescents in the Western Cape of South Africa were enrolled and assigned to three study arms. While neither vaccine arm demonstrated statistically significant protection against IGRA conversion compared to the placebo, BCG revaccination exhibited 45.4% efficacy in preventing sustained IGRA conversion, which was interpreted as preventing latent TB infection. In contrast, H4:IC31 had only 30.5% efficacy, leading to the termination of this arm of the study. Interestingly, BCG revaccination upregulated Th1 and IL-22 producing CD4 T cell responses, along with a modest increase in IFNγ-producing natural killer (NK) cells. Ongoing efforts are underway to validate the efficacy of BCG revaccination in a larger cohort of 1800 South African adolescents (NCT04152161), with an expected completion date in early 2026. These results demonstrate a potential new use for BCG in protecting high-risk populations from becoming infected with *M. tuberculosis*.

EndTB clinical trial

Obiettivo:

valutare l'efficacia e la sicurezza di 5 trattamenti orali da 9 mesi per il trattamento di TB polmonare rifampicino-resistente

Metodi:

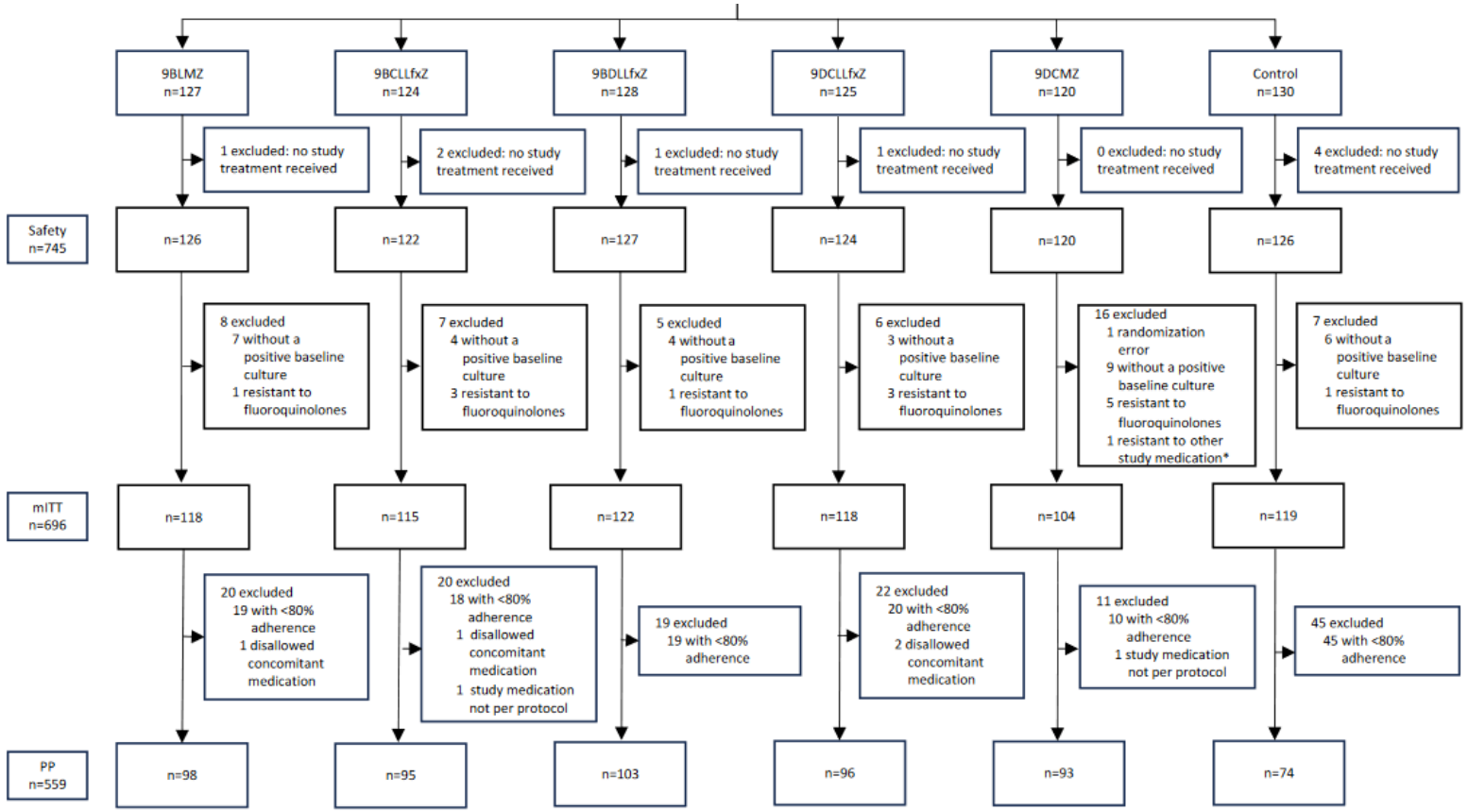
sono stati arruolati tutti i pazienti di età >15 anni con TB polmonare rifampicino-resistente con mantenuta sensibilità ai fluorochinoloni.

I pazienti sono stati poi randomizzati in rapporto 1:1:1:1:1:1 ai vari regimi proposti con eventuali adattamenti alla luce del test di resistenza fenotipica al colturale

Trial regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Fluoroquinolone	Pyrazinamide
9BLMZ	B			L	M	Z
9BCLLfxZ	B		C	L	Lfx	Z
9BDLLfxZ	B	D		L	Lfx	Z
9DCLLfxZ		D	C	L	Lfx	Z
9DCMZ		D	C		M	Z
Control	Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis. Composed according to latest World Health Organization guidelines, as they evolved during the trial. This group included mostly participants treated with the 18-month conventional regimen.					

EndTB clinical trial

Sono stati arruolati un totale di 754 pazienti



mITT modified-intention-to-treat, PP per protocol

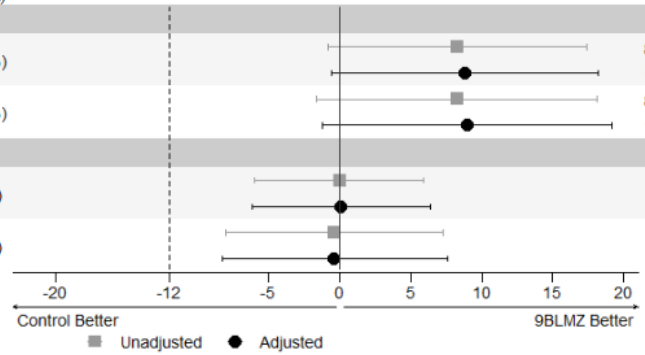
EndTB clinical trial

Outcome	9BLMZ (N = 98)	9BCLLfxZ (N = 95)	9BDLLfxZ (N = 103)	9DCLLfxZ (N = 96)	9DCMZ (N = 93)	Control (N = 74)	Total (N = 559)
Favorable							
Participants - no. (%)	94 (95.9%)	91 (95.8%)	97 (94.2%)	82 (85.4%)	82 (88.2%)	71 (95.9%)	517 (92.5%)
Absolute difference from control (%, 95% CI)	0.0% (-6.0%;5.9%)	-0.2% (-6.2%;5.9%)	-1.8% (-8.1%;4.6%)	-10.5% (-18.9%;-2.2%)	-7.8% (-15.7%;0.2%)	--	--
Participants with negative culture results, Week 65 and 73 – no. (%)	93 (94.9%)	88 (92.6%)	95 (92.2%)	80 (83.3%)	81 (87.1%)	69 (93.2%)	506 (90.5%)
Participants with favorable bacteriological, clinical and radiological evolution^^ – no. (%)	1 (1.0%)	3 (3.2%)	2 (1.9%)	2 (2.1%)	1 (1.1%)	2 (2.7%)	11 (2.0%)
Unfavorable							
Participants – no. (%)	4 (4.1%)	4 (4.2%)	6 (5.8%)	14 (14.6%)	11 (11.8%)	3 (4.1%)	42 (7.5%)
Death, all cause – no. (%)££	2 (2.0%)	0 (0.0%)	3 (2.9%)	3 (3.1%)	2 (2.2%)	2 (2.7%)	12 (2.1%)
Participants with positive culture results** – no. (%)	1 (1.0%)	2 (2.1%)	1 (1.0%)	10 (10.4%)	4 (4.3%)	1 (1.4%)	19 (3.4%)
Participants with unfavorable bacteriological, clinical and/or radiological evolution^^ – no. (%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	2 (0.4%)
Participants with recurrence§§ – no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)	0 (0.0%)	2 (0.4%)
Participants with permanent treatment discontinuation due to adverse event – no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Participants with poor treatment adherence/lost to follow-up – no. (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.2%)
Participants who withdrew consent – no. (%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Participants with other unfavorable outcome## – no. (%)	1 (1.0%)	1 (1.1%)	1 (1.0%)	1 (1.0%)	1 (1.1%)	0 (0.0%)	5 (0.9%)

EndTB clinical trial

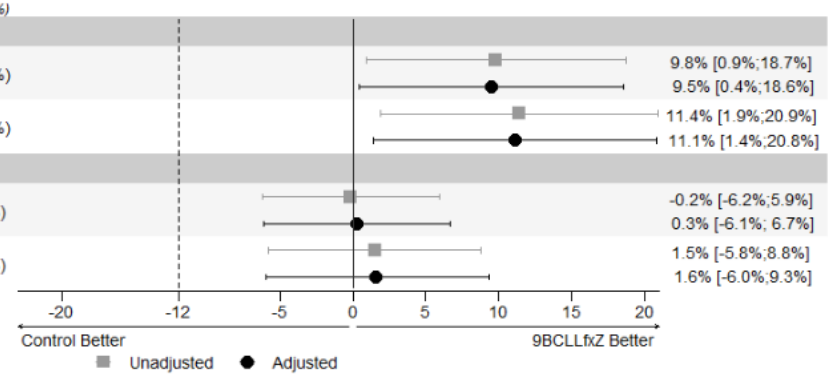
9BLMZ vs. Control

Analysis population	9BLMZ	Control	Risk Difference with 95% Confidence Interval
	no. with favorable outcome/total no. (%)		
mITT			
W73	105/118 (89.0%)	96/119 (80.7%)	8.3% [-0.8%;17.4%] 8.8% [-0.6%;18.2%]
W104	101/118 (85.6%)	92/119 (77.3%)	8.3% [-1.6%;18.1%] 9.0% [-1.2%;19.2%]
PP			
W73	94/98 (95.9%)	71/74 (95.9%)	0.0% [-6.0%;5.9%] 0.1% [-6.2%; 6.4%]
W104	91/98 (92.9%)	69/74 (93.2%)	-0.4% [-8.0%;7.3%] -0.4% [-8.3%;7.6%]



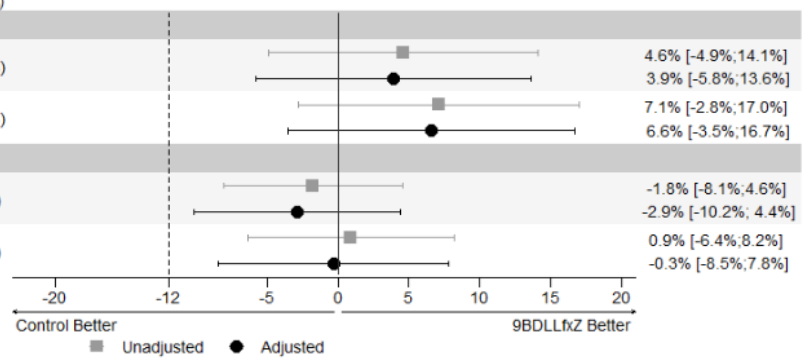
9BCLLfxZ vs. Control

Analysis population	9BCLLfxZ	Control	Risk Difference with 95% Confidence Interval
	no. with favorable outcome/total no. (%)		
mITT			
W73	104/115 (90.4%)	96/119 (80.7%)	9.8% [0.9%;18.7%] 9.5% [0.4%;18.6%]
W104	102/115 (88.7%)	92/119 (77.3%)	11.4% [1.9%;20.9%] 11.1% [1.4%;20.8%]
PP			
W73	91/95 (95.8%)	71/74 (95.9%)	-0.2% [-6.2%;5.9%] 0.3% [-6.1%; 6.7%]
W104	90/95 (94.7%)	69/74 (93.2%)	1.5% [-5.8%;8.8%] 1.6% [-6.0%;9.3%]



9BDLLfxZ vs. Control

Analysis population	9BDLLfxZ	Control	Risk Difference with 95% Confidence Interval
	no. with favorable outcome/total no. (%)		
mITT			
W73	104/122 (85.2%)	96/119 (80.7%)	4.6% [-4.9%;14.1%] 3.9% [-5.8%;13.6%]
W104	103/122 (84.4%)	92/119 (77.3%)	7.1% [-2.8%;17.0%] 6.6% [-3.5%;16.7%]
PP			
W73	97/103 (94.2%)	71/74 (95.9%)	-1.8% [-8.1%;4.6%] -2.9% [-10.2%; 4.4%]
W104	97/103 (94.2%)	69/74 (93.2%)	0.9% [-6.4%;8.2%] -0.3% [-8.5%;7.8%]



Clofazimine safety/efficacy in NTM-PD

Obiettivo:

valutare l'efficacia e la sicurezza del trattamento con clofazimina in base ai parametri di farmacocinetica nel trattamento delle malattie polmonari da micobatteri non tubercolari

Metodi:

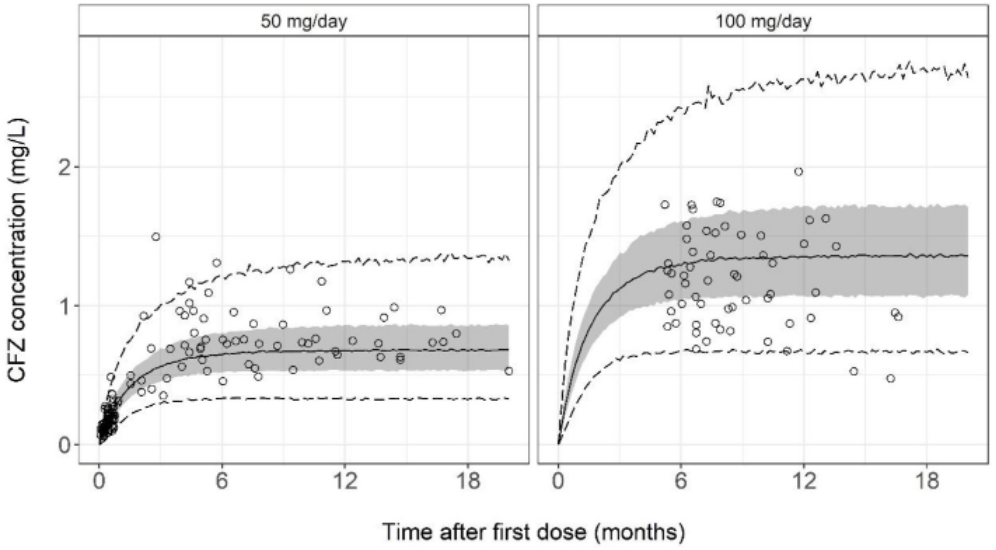
sono stati arruolati tutti i pazienti di età >20 anni con malattia polmonare attiva da micobatteri dell'avium complex, M. abscessus e massiliense. Sono stati esclusi dall'analisi i pazienti che hanno sospeso clofazimina prima di 6 mesi e le pazienti in gravidanza.

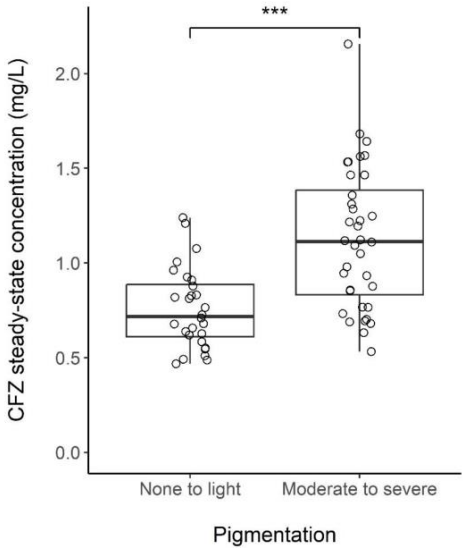
I pazienti arruolati sono stati trattati con un dosaggio di 100 mg die, mentre quelli con dosaggio di 50 mg die sono stati ottenuti da uno studio osservazionale dello stesso ospedale.

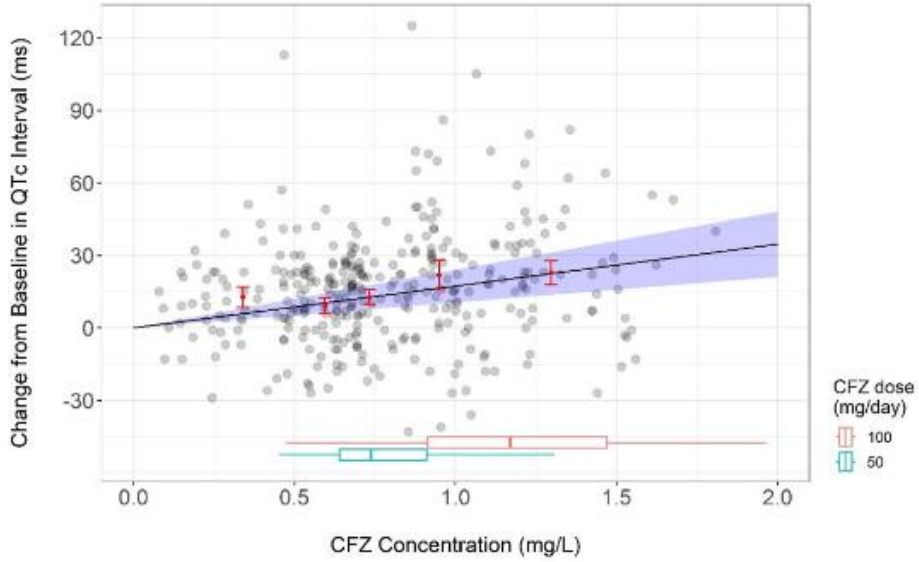
Sono stati arruolati un totale di 71 pazienti. Di questi 7 sono stati esclusi per aver interrotto la clofazimina entro i primi 2 mesi.

Dei restanti 64: 35 (54,7%) hanno ricevuto un dosaggio giornaliero di 50 mg e 29 (45,3%) un dosaggio di 100 mg.

Clofazimine safety/efficacy in NTM-PD







Clofazimine safety/efficacy in NTM-PD

La conversione del colturale è stata raggiunta in 33 pazienti (51.6%) con un tempo mediano di 2,5 mesi.

Predictors of conversion among patients treated over 6 months (N = 64).

Variables	With culture conversion (N = 33)	Without culture conversion (N = 31)	Univariable *P*-value	Multivariate analysis	
				aOR (95 % CI)	*P*-value
Age	61.1 ± 11.8	65.2 ± 8.4	0.116		
Male sex	7 (21.2 %)	4 (12.9 %)	0.383		
Sputum smear positivity	16 (48.5 %)	21 (67.7 %)	0.122		
MAC	14 (42.4 %)	20 (64.5 %)	0.079		
M. abscessus	11 (33.3 %)	8 (25.8 %)	0.511		
M. massiliense	10 (30.3 %)	3 (9.7 %)	0.051		
Cavitation	20 (60.6 %)	23 (74.2 %)	0.250		
Surgery	9 (27.3 %)	2 (6.5 %)	0.041	5.4 (1.3–38.0)	0.041
Macrolide resistance	18 (54.5 %)	21 (67.7 %)	0.281		
MIC of CFZ ≤0.25 mg/L	16 (48.5 %)	18 (58.1 %)	0.200		
CFZ Css	1.0 ± 0.4	0.9 ± 0.3	0.129		

95 % CI, 95 % confidence interval; aOR, adjusted odds ratio; Css, steady-state concentration; MIC, minimum inhibitory concentration.

Grazie per l'attenzione