OPEN ACCESS

Saudi Journal of Medicine
Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) | ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Fungal Infections in Spondyloarthritis Patients Undergoing Biotherapy: Insights from the Moroccan Biotherapy Registry (RBSMR) over a Three-Year Follow-Up Period

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DOI: https://doi.org/10.36348/sjm.2024.v09i09.001 | **Received:** 24.07.2024 | **Accepted:** 30.08.2024 | **Published:** 02.09.2024

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Abstract

Biological therapy increases the risk of fungal infections in chronic inflammatory rheumatism patients. ***Objectives*:** To determine the incidence of fungal infections in spondyloarthritis patients on biotherapy in the Moroccan registry (RBSMR) during 3-year follow-up and to identify associated factors. ***Methods*:** Patients' socio-demographic, clinical and para-clinical data were collected. The type of biotherapy used and episodes of fungal infections were determinated. Also, the frequency of corticosteroids and NSAIDs use, disease activity, and various comorbidities before and at the time of fungal infection during the 3 years of follow-up were defined. Regarding fungal infection, the germ and location were specified. ***Results*:** Seven spondyloarthritis patients out of 194 had a fungal infection (with 8 episodes). Mean age was 44±17 years, with mean disease duration of 11 years. All these patients had comorbidities before and during the fungal infection. At the time of this, all patients were on TNF alpha inhibitors, specifically, one patient was on Adalimumab but later switched to Etanercept, five were on Etanercept, and one was on Infliximab. No case of systemic fungal infection was noted. In the 8 fungal infection episodes, there were 7 cases of appendages' involvement and 1 case of vaginal candidiasis. ***Conclusion*:** The incidence of fungal infections in patients with spondyloarthritis remains low and seems to be related to disease activity and type of biologics.

Keywords: Fungal Infections, Biotherapy, chronic inflammatory rheumatism, spondyloarthritis, NSAIDs.

INTRODUCTION

The use of biotherapy has significantly transformed the management and outcomes of patients with inflammatory rheumatic diseases. Biologics have become increasingly popular, but they may have reversible side effects that can lead to treatment discontinuation. Fungal infections are one potential side effect [1].

Fungi are a crucial component of the human microbiome. However, in individuals with weakened immune systems, some fungi can become pathogenic. These opportunistic pathogens typically cause localized and benign infections in healthy individuals. However,

in immunocompromised conditions, such as in patients receiving immunomodulatory treatments, these infections can lead to systemic morbidity and increased mortality [2].

Research into the risk of fungal infections associated with biotherapies has mainly focused on patients with rheumatoid arthritis. Although these infections are relatively uncommon, they represent a small proportion of serious or opportunistic infections [3].

To improve our understanding of the infectious risk associated with biotherapy, particularly fungal infections in patients with spondyloarthritis, we conducted this study, which aimed to determine the incidence of fungal infections in patients with spondyloarthritis who received biotherapy in the RBSMR (biotherapy registry of the Moroccan Society of Rheumatology) over a three-year follow-up period. In addition, it aimed to identify factors associated with these infections.

METHODS

- **RBSMR Registry**

Our study was based on data from the RBSMR (Registre des Biothérapies de la SociétéMarocaine de Rhumatologie), a multicentre historical-prospective registry of patients over 18 years old who were initiating or undergoing biotherapy for rheumatoid arthritis (RA) or spondyloarthritis (SpA). 440 patients were enrolled, with 419 meeting validation criteria (225 with RA and 194 with SpA), between May 2017 and January 2019. The rheumatology departments of all ten university hospitals in Morocco participated in the study. Data on efficacy and tolerance were recorded systematically every six months, as well as whenever patients experienced adverse events or underwent a change in treatment [4].

- **Inclusion and exclusion criteria**

This is a three-year follow-up study that included 194 SpA patients who were over 18 years old, diagnosed according to ASAS (Assessment of SpondyloArthritis international Society) 2009 criteria and receiving biologics. All participants provided written informed consent. Patients receiving biotherapy for other indications and those diagnosed with juvenile idiopathic arthritis were excluded.

- **Fungal infection diagnosis**

The diagnosis of fungal infection was determined through either expert opinion or microbiological examination.

- **Statistical analysis**

Parameters with a normal distribution were reported as mean ± standard deviation (SD), while asymetric parameters were expressed as median ± interquartile range (IQR), defined as the 25th to 75th percentiles. Qualitative data were estimated as frequencies (number and percentage). To compare patients with fungal infections to those without, we used the t-student test for continuous variables with a normal distribution and the Mann-Whitney test for those with an asymmetric distribution. For categorical variables, we used the Chi-square test or Fischer's exact test. The statistical significance threshold was set at 0.05. We performed the statistical analysis using SPSS software, version 13.0.

- **Ethics approval and consent to participate**

Both local institutional review boards and the national ethics committee, specifically the Ethics Committee for Biomedical Research of the University Mohammed V of Rabat, Faculty of Medicine and Pharmacy, under reference number 958/09/19 on September 11, 2019, approved the RBSMR study protocol. All participating patients provided written informed consent for publication of study results.

RESULTS

A total of 194 SpA patients were included in the study. Table 1 lists the socio-demographic, clinical, and therapeutic characteristics. The median age of the patients was 40,23 ±13,68 years, with a male predominance (63.4%), and the mean disease duration was 12,83 ± 7,27years. Regarding comorbidities, 5.7% had diabetes, and 5.2% had hypertension. The mean BASDAI was 3.2±2.11, and the mean ASDAS CRP was 2.21±1.99, indicating moderate disease activity.

During the 3-year follow-up period, 7 (3.6%) patients with SpA were diagnosed with fungal infections, comprising 4 men and 3 women. The mean age of these patients during the infection was 44±17.23 years.

At baseline and during the fungal infection, all these participants had an active disease with a mean BASDAI of 4.88±0.637 and 2.80±1.27, respectively, and a mean ASDAS CRP of 3.60±0.804 and 2.42±1.25, as detailed in Tables 2 and 3.

During the fungal infection, only one patient was taking corticosteroids and another was taking NSAIDs. No conventional synthetic disease-modifying antirheumatic drugs (CsDMARDS), such as methotrexate, were administered.

Six patients received TNF alpha inhibitors, with five taking Adalimumab, one taking Etanercept and one patient was taking Secukinumab at baseline. At the time of infection all patients were receiving TNF-α inhibitors. Specifically, one patient was on Adalimumab but later switched to Etanercept, five were on Etanercept, and one was on Infliximab. Interestingly, two patients had changed their biologic treatments more than twice before the infection occurred. Although temporary treatment

interruption was advised, none of the seven patients switched medications.

The study identified eight fungal infections (one patient between the seven cases mentioned above had experienced two fungal infections). The infections were located in various areas: 3 on the soles of the feet and between the toes, 2 only between the toes, 2 on the toenails, and 1 in the vaginal area. The responsible pathogens were identified in two cases: Candida albicans and Trichophyton rubrum. However, no systemic fungal infections were detected.

Table 1: Characteristics of study population at baseline

	Total (n=194)
Age (years)	40,23 ±13,68
Men	123 (63,4)
BMI (Body Mass Index)	25,26 ±7,9
High blood pressure	11 (5,6)
Diabetes	10 (5,1)
Smoking	21 (6.6)
Type of treatment	
Corticosteroids	34 (22,2)
CsDMARDs	107 (55,2)
Infliximab	53 (27,31)
Adalimumab	67 (34,53)
Golimumab	31 (15,79)
Etanercept	74 (38,14)
Secukinumab	8 (4,12)
Ustekinumab	1 (0,51)
Duration of biotherapy exposure in years	5,68 ± 2,39
Duration of disease	12,83 ± 7,27
Axial form	186 (95,9)
Peripheral form	133 (68,6)
Enthesitic form	115 (59,3)
Radiographic form	170 (87.6)
HLA B27	35 (18)
IBD (inflammatory bowel disease)	20 (10.2)
Psoriasis	13 (6.7)
Uveitis	27 (13.9)
BASDAI	3,2± 2,11
ESR (erythrocyte sedimentation rate)	35 [17-55]
CRP (C-reactive protein)	20 [7-45]
ASDAS CRP	2,21± 1,99

Table 2: Description of fungal infection cases at the time of the infection episode

Case &N° in database	1 (20)	2 (30)	3 (30)	4 (37)	5 (38)	6 (58)	7 (83)	8 (151)
Age	72	28	28	35	34	39	60	65
Gender	M	M	M	M	M	F	F	F
Duration of disease (years)	23	17	17	10	15	4	12	11
SpA phenotype	Axial and pheripheral	Axial and peripheral	Axial and peripheral	Axial	Axial	Axial and enthesitic	Axial ethesitic & peripheral	Peripheral &enthesitic
Diabetes	No	No	No	No	No	No	No	**Yes**
Smoking	No	No	No	No	No	No	No	No
CTC	No	No	No	No	No	No	No	**Yes**
NSAIDs	**Yes**	No	No	No	No	No	No	No
CsDMARDS	No	No	No	No	No	No	No	No
bDMARDS	Etanercept	Adalimumab	Etanercept	Etanercept	Infliximab	Etanercept	Etanercept	Etanercept
Duration of biotherapy exposure (years)	-	0,16	-	-	-	-	-	6

Number of biotherapy switches > 2	No	No	**Yes**	No	No	No	No	**Yes**
BASDAI	1.5	4.8	-	1.4	-	3.5	2.8	-
ASDAS CRP	3.9	3.8	-	1.1	-	2.3	1	-
Germidentified	***Trichophyton Rubrum***	-	-	-	-	***Candida***	-	-
localization	Nails	Toes & sole of the feet	Toes & sole of the feet	Toes	Toes & sole of the feet	Vaginal	Nails	Toes

Table 3: Comparison between the two groups: Group with fungal infection and group without fungal infection based on baseline characteristics

	Fungal Infection (n=7)	**No-Fungal Infection (n=187)**	**P**
Age	44±17,23	40 +-13,54	0.79
Men	4 (62,5%)	119(63,6%)	0.47
Duration of disease in years	12,5±4,90	11,84±6,79	0.53
SpA phenotype	-Axial 6 (3%) -Peripheral 4 (2%) -Enthesitic 3 (1,5 %)	- 186 (95,9%) - 133 (68,6%) -115 (59,3%)	0.67 0.65 0.60
Diabetes	1 (12,5%)	9(4,81%)	0.83
BMI	25,021±6,977	25,26 ±7,9	0,73
Smoking	1 (14,28 %)	21 (6.6%)	0,77
CTC	1 (12,5%)	41(22,3%)	0.25
NSAIDs	1 (12,5%)	37 (19,8%)	0.31
BASDAI	4,88±0.637	3,2±2,11	0.79
ASDAS CRP	3.60±0.804	3,4±1,46	0.14
BASFI	4,9±2,9	3,7±3,07	0,36
Duration of biotherapy exposure in years	3,08±4,13	5,68 ± 2,39	0,37

DISCUSSION

Over three years of follow-up, the observed incidence of fungal infections in SpA patients recruited to the RBSMR was 10/1000 patient-year. To compare data concerning fungal infections in SpA patients receiving biologic therapy, our literature review revealed limited information. Clear incidence rates for these infections were not available. However, a significant number of case reports were identified in the literature [5]. In fact, data on fungal infections in spondyloarthritis remains scarce or non-existent in the literature. To fill this knowledge gap, additional studies with longer follow-up periods are needed to improve our knowledge of the incidence and characteristics of fungal infections in patients with spondyloarthritis.

When it comes to fungal infections in RA patients recruited in the same registry, we found six patients out of 225 who had reported a fungal infection, which corresponded to an incidence rate of 8/1000 patient-year. Once again, it was difficult to compare these findings with the existing literature because of the lack of clear incidence rates, which were often based on case reports.

Interestingly, no statistically significant associations were identified between demographic, clinical, or therapeutic characteristics and the occurrence of fungal infections in this study. However, it is important to note that all of the seven patients were receiving TNF-α inhibitors and had disease activity at the time of infection. Among the cases identified, only one patient was receiving corticosteroids, another was taking nonsteroidal anti-inflammatory drugs (NSAIDs), and one patient had diabetes. These findings highlight the complexity of factors contributing to fungal infections in this patient population, including use of specific medications, rheumatic disease activity, and individual health conditions. As there was no clear data on the factors associated with the occurrence of these infections in SpA patients under biotherapy, we were unable to compare the results of our study with those in the literature.

Nevertheless, the potential impact of biologics on patients' susceptibility to opportunistic fungal infections had attracted significant attention when the Food and Drug Administration (FDA) issued a black box warning in 2001. This warning specifically addressed the risk of histoplasmosis associated with TNF-α inhibitors. This warning was issued following the reporting of 240 cases of histoplasmosis in people receiving treatment with these drugs [6].

In our study, all patients who experienced fungal infections were receiving TNF-α inhibitors at the time of infection. Specifically, one patient was on Adalimumab but later switched to Etanercept, five were on Etanercept, and one was on Infliximab. Interestingly, two patients had changed their biologic treatments more

than twice before the infection occurred. As indicated above, we had identified eight fungal infections, two of which were specifically documented: a case of vaginal candidiasis and a case of Trichophyton rubrum onychomycosis. Both of these patients were on Etanercept at the time of the infection.

Vallabhaneni and Chiller, in a 2016 systematic review, reported several findings related to fungal infections in patients undergoing biologic treatments for several rheumatic diseases. For TNF-α inhibitors, an increased risk was noted for Adalimumab and Infliximab compared to Etanercept, with a specific alert for histoplasmosis and other endemic fungal infections [7-10]. Golimumab was linked to reported cases of coccidioidomycosis [11, 12]. For Certolizumab, it has been reported multiple fungal infections including candidiasis, Pneumocystis Jirovecii Pneumonia (PJP), histoplasmosis [13, 14]. For biologic agents targeting IL-17, Secukinumab was associated with a 2-5% risk of candidiasis, especially in oral, esophageal, cutaneous, or vaginal localizations, and Ixekizumab had an even higher risk [15, 16]. In a meta-analysis of randomized clinical trials conducted by Lidong Hu *et al*., a higher risk of Candida infection in peripheral SpA patients treated with IL-17 inhibitors was observed (OR: 2.52, 95% CI: 1.31-4.84, P=0.006) [3]. The occurrence of Candida infections is closely associated with the use of biologic agentsinhibitors of IL17 such as Secukinumab and Ixekizumab. Moreover, Ustekinumab did not show any reported cases of fungal infections [6]. For Tofacitinib, it had reported cases of esophageal candidiasis and cryptococcal infection for both RA and PsA patients [17, 18].

It is crucial to emphasize that no systemic fungal infections were documented between our cases. Localizations included mainly the toenails, the toes, the soles of the feet and the vaginal area. It is therefore important to recognize that this is an important limitation of our study, given that all these infections were only recorded as case reports from our registry, without specifying the imput ability of the biological agent, and were known common in the general population. In addition, they did not represent the typical fungal infections commonly associated with TNF-α inhibitors.

Specific fungal diseases like Candidiasis [19], Pneumocystis jirovecii pneumonia (PJP) [20], Aspergillosis [21, 22], and Dermatophytosis [23, 24] including Pityriasis, Tinea, and Trichophyton, as well as Histoplasmosis [25], remain strongly linked to TNF-α inhibitors. However, obtaining data on other fungal infections among patients taking biologics, such as Cryptococcus [26], Coccidioidomycosis [27], Blastomycosis, and other endemic mycoses [28], is challenging due to the small number of reported infections.

Finally, the main limitation of our study was the small sample compared to a national registry whose data collection inherently introduces the possibility of missing information. However, this is the first multicenter research of this scale and type, specifically designed to study rheumatic diseases subject to biotherapy in Morocco and the broader North African region. This unique feature reinforces its importance within the scientific community, providing valuable information on the management and outcomes of biotherapy in this particular population. In addition, our study focused on fungal infections in SpA patients for which data is lacking in the literature.

CONCLUSION

The incidence of fungal infections in spondyloarthritis patients receiving biotherapy was 10/1000 patient-year in our study. Seven patients with fungal infections were on TNF-α inhibitors and had active disease before and after infection. However, it is important to know that data relating to fungal infections in spondyloarthritis patients undergoing biotherapy are currently limited or even non-existent in the literature. This highlights the need for larger studies with prolonged follow-up periods to better understanding the incidence and characteristics of fungal infections in this specific patient population.

REFERENCES

1. Fleury, G. R. E. G. O. R. Y., & Gabay, C. (2017). Effets secondaires des traitements biologiques. *Rev Med Suisse*, *13*, 542-548. Doi: 10.53738/REVMED.2017.13.553.0542.
2. Lass-Flörl, C. (2017). Human fungal pathogen identification: Methods and protocols, book 2017, ed. Thomas Lion, Springer New York, NY, pp. 3–15. https://doi.org/10.1007/978-1-4939-6515-1
3. Hu, L., Man, S., Ji, X., Wang, Y., Liu, X., Zhang, J., ... & Huang, F. (2022). Risk of infections of biological and targeted drugs in patients with spondyloarthritis: meta-analysis of randomized clinical trials. *Chinese Medical Journal*, *135*(08), 911-919. doi: 10.1097/CM9.0000000000001928
4. Hmamouchi, I., Abouqal, R., Achemlal, L., Allali, F., Bahiri, R., & El Bouchti, I. (2019). The Moroccan registry of biological therapies in rheumatic diseases (RBSMR): methods and preliminaries results. *Rev Mar Rhum*, *49*, 32-37.
5. Tong, Q., Cai, Q., De Mooij, T., Xu, X., Dai, S., Qu, W., & Zhao, D. (2015). Adverse events of anti-tumor necrosis factor α therapy in ankylosing spondylitis. *PLoS One*, *10*(3), e0119897.
6. FDA. (2001). http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113512.htm.Accessed Jan 29, 2016.
7. Vallabhaneni, S., & Chiller, T. M. (2016). Fungal infections and new biologic therapies. *Current*

rheumatology reports, *18*, 1-10. Doi: 10.1007/s11926-016-0572-1.

8. Bongartz, T., Sutton, A. J., Sweeting, M. J., Buchan, I., Matteson, E. L., & Montori, V. (2006). Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *Jama*, *295*(19), 2275-2285. doi:10.1001/jama.295.19.2275.
9. Ford, A. C., & Peyrin-Biroulet, L. (2013). Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. *Official journal of the American College of Gastroenterology| ACG*, *108*(8), 1268-1276. doi:10.1038/ ajg.2013.138.
10. Galloway, J. B., Hyrich, K. L., Mercer, L. K., Dixon, W. G., Fu, B., Ustianowski, A. P., ... & Symmons, D. P. (2011). Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology*, *50*(1), 124-131. doi:10.1093/ rheumatology/keq242.
11. Kay, J., Fleischmann, R., Keystone, E., Hsia, E. C., Hsu, B., Mack, M., ... & Kavanaugh, A. (2015). Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. *Annals of the rheumatic diseases*, *74*(3), 538-546. doi:10.1136/ annrheumdis-2013-204195.
12. Sandborn, W. J., Feagan, B. G., Marano, C., Zhang, H., Strauss, R., Johanns, J., ... & PURSUIT-SC Study Group. (2014). Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*, *146*(1), 85-95. doi: 10.1053/j.gastro.2013.05.048.
13. Bykerk, V. P., Cush, J., Winthrop, K., Calabrese, L., Lortholary, O., De Longueville, M., ... & Mariette, X. (2015). Update on the safety profile of certolizumab pegol in rheumatoid arthritis: an integrated analysis from clinical trials. *Annals of the rheumatic diseases*, *74*(1), 96-103. doi: 10. 1136/annrheumdis-2013-203660.
14. Sandborn, W. J., Lee, S. D., Randall, C., Gutierrez, A., Schwartz, D. A., Ambarkhane, S., ... & Lichtenstein, G. R. (2014). Long-term safety and efficacy of certolizumab pegol in the treatment of Crohn's disease: 7-year results from the PREC i SE 3 study. *Alimentary pharmacology & therapeutics*, *40*(8), 903-916. doi:10.1111/apt.12930.
15. Langley, R. G., Elewski, B. E., Lebwohl, M., Reich, K., Griffiths, C. E., Papp, K., ... & Papavassilis, C. (2014). Secukinumab in plaque psoriasis—results of two phase 3 trials. *New England Journal of Medicine*, *371*(4), 326-338. doi:10.1056/NEJMoa1314258.
16. Griffiths, C. E., Reich, K., Lebwohl, M., Van De Kerkhof, P., Paul, C., Menter, A., ... & Papp, K. (2015). Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *The Lancet*, *386*(9993), 541-551. doi:10.1016/ s0140-6736(15)60125-8.
17. Kremer, J., Li, Z. G., Hall, S., Fleischmann, R., Genovese, M., Martin-Mola, E., ... & Bradley, J. (2013). Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Annals of internal medicine*, *159*(4), 253-261. doi:10.7326/0003-4819-159-4-201308200- 00006.
18. Winthrop, K. L., Park, S. H., Gul, A., Cardiel, M. H., Gomez-Reino, J. J., Tanaka, Y., ... & Valdez, H. (2016). Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. *Annals of the rheumatic diseases*, *75*(6), 1133-1138. doi: 10.1136/annrheumdis-2015-207319.
19. Filler, S. G., Yeaman, M. R., & Sheppard, D. C. (2005). Tumor necrosis factor inhibition and invasive fungal infections. *Clinical infectious diseases*, *41*(Supplement_3), S208-S212. doi:10.1086/430000.
20. Grubbs, J. A., & Baddley, J. W. (2014). Pneumocystis jirovecii pneumonia in patients receiving tumor-necrosis-factor-inhibitor therapy: implications for chemoprophylaxis. *Current rheumatology reports*, *16*(10), 445. doi:10.1007/s11926-014-0445-4.
21. Arnold, T. M., Sears, C. R., & Hage, C. A. (2009). Invasive fungal infections in the era of biologics. *Clinics in chest medicine*, *30*(2), 279-286. doi: 10.1016/ j.ccm.2009.02.007. vi.
22. Nedel, W. L., Kontoyiannis, D. P., & Pasqualotto, A. C. (2009). Aspergillosis in patients treated with monoclonal antibodies. *Revista iberoamericana de micologia*, *26*(3), 175-183. doi: 10.1016/j.riam.2009.04.001.
23. Bardazzi, F., Balestri, R., Rech, G., Antonucci, A., & Patrizi, A. (2011). Dermatophytosis during anti-TNF-α monoclonal antibody therapy. *Mycoses*, *54*(5), e619–620. doi: 10.1111/j.1439-0507.2010.01930.x.
24. Balestri, R., Rech, G., Piraccini, B. M., Antonucci, A., Ismaili, A., Patrizi, A., & Bardazzi, F. (2012). Pityriasis versicolor during anti-TNF-α monoclonal antibody therapy: therapeutic considerations. *Mycoses*, *55*(5), 444-446. doi:10.1111/j.1439-0507. 2012.02170.x
25. Winthrop, K. L., Yamashita, S., Beekmann, S. E., Polgreen, P. M., & Infectious Diseases Society of America Emerging Infections Network. (2008). Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and

other newly approved biologic therapies: case finding through the Emerging Infections Network. *Clinical infectious diseases*, *46*(11), 1738-1740. doi: 10.1086/587989.

26. Tsiodras, S., Samonis, G., Boumpas, D. T., & Kontoyiannis, D. P. (2008, February). Fungal infections complicating tumor necrosis factor α blockade therapy. In *Mayo Clinic Proceedings* (Vol. 83, No. 2, pp. 181-194). Elsevier.
27. Bergstrom, L., Yocum, D. E., Ampel, N. M., Villanueva, I., Lisse, J., Gluck, O., ... & Yung, C. M. (2004). Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor α antagonists. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, *50*(6), 1959-1966. doi:10.1002/art.20454.
28. Salt, E., Wiggins, A. T., Rayens, M. K., Huaman, M. A., Mannino, D., Schwieterman, P., ... & Crofford, L. J. (2016). Risk factors for targeted fungal and mycobacterial infections in patients taking tumor necrosis factor inhibitors. *Arthritis & Rheumatology*, *68*(3), 597-603.