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Patients with Arthritis Undergoing Surgery: How Should We Manage Tumour Necrosis Factor Blocking Agents Perioperatively?-A Systematic Literature Review

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We systematically reviewed the literature on the infectious risk in patients treated with tumour necrosis factor blocking agents (TNF-BA) undergoing surgery: we searched the Medline (PubMed) and the online archive from the Annual European Congress of Rheumatology and the Annual Scientific Meeting of the American College of Rheumatology. Of total 1259 reports, 14 were finally analysed. With one exception all were retrospective. Four of 6 studies compared patients on TNF-BA with those not receiving TNF-BA, and found an increased risk of infection with the use of TNF-BA. None of the other studies which compared continued with discontinued treatment at surgery found an increased risk of infection, when the medication was continued perioperatively. In conclusion, while in theory there is an increased risk of infections when TNF-BA are administered perioperatively, the available literature does not necessarily support this. It rather appears that patients receiving TNF-BA are a *priori* at a higher risk of postoperative infections. Scheduling surgery at the end of the drug interval and adding one "safety" week prior to surgery should be an acceptable plan in daily clinical practice.

Key Words: Surgery, arthritis, tumour necrosis factor blocking agents, infection

The introduction of tumour necrosis factor blocking agents (TNF-BA) into the care of patients with arthritis substantially improved treatment options. While these drugs reduce disease activity and joint damage, they can also pose a generally increased risk of infection.[1] Despite modern medical therapies surgery is still common in patients with rheumatoid arthritis (RA).[2] Thus, when patients treated with TNF-BA elect surgery, the challenging question arises of how best to manage this medication perioperatively: on the one hand, continuing treatment might in-

crease the risk of perioperative infections. On the other hand, discontinuation could lead to a disease flare that can limit postoperative rehabilitation and to the need for corticosteroids, which in turn have unfavourable side effects on wound healing. We have previously presented a review on the perioperative management of anti-rheumatic medication.[3] Controversy on how TNF-BA can best be managed is ongoing, therefore, we decided to systematically review the literature on the infectious risk in patients treated with TNF-BA and summarized available data herein.

We performed a Medline (PubMed) search of the English-language literature from the earliest entries to 2010. The following index keywords were used: "arthritis" and ("surgery" or "perioperative") and ("infliximab" or "adalimumab" or "etanercept" or "certolizumab" or "golimumab" or "tumour necrosis factor"). In addition, we searched the online archive from the Annual European Congress of Rheumatology and the Annual Scientific Meeting of the American College of Rheumatology (ACR). References in retrieved articles were searched for further relevant studies. If both a full text and an abstract were available, only the full text was used for analysis.

For the analysis, we accepted all relevant studies, whether prospective or retrospective. In addition, we included case series with ≥10 patients. Those series with fewer than 10 patients were excluded, as we considered such reports not to provide sufficient information. Not included in the analysis were reviews, commentaries, editorials, letters to the editor (except for such with original data) or case reports. Fig. 1 shows the flow chart of article selection.

In general, the studies were of two types: the one type compared patients on TNF-BA with patients not receiving this treatment ["yes/no" studies; (y/n)]. In the second study type, all patients received TNF-BA: in these studies one group of patients continued treatment during surgery, while patients in the other group discontinued treatment ["continued/discontinued" studies; (c/disc)]. Three of the studies looked at 3 groups; one group discontinuing treatment with TNF-BA at surgery, one continuing this treatment and a third group that did not receive these agents. For these studies we present the data in both forms, as a y/n study and as a c/disc study; for the y/n presentation, all the patients on TNF-BA were grouped together, regardless of whether treatment was stopped at surgery or not.

Fourteen reports were analyzed. With one exception[4] all were retrospective.[2,5-16] Nine reports were published as studies,[2,4-11] and five reports were published only as abstracts.[12-16] There were 6 y/n studies, 3 c/disc studies, and 3 papers that presented data both in a y/n and c/disc form. Two abstracts presented large case series. Nearly all participants in the studies had RA. Most procedures performed were orthopaedic surgeries. Four studies (all of them of the y/n type) found an increased risk of infection with the use of TNF-BA whereas none of the other studies did find the increased risk. None of the c/disc studies found an increased risk of infection, when the medication was continued perioperatively. All data are summarized in Table 1.

In sum, the results of the studies would indicate that the perioperative continuation of TNF-BA does not add substantial risk of infection. However, patients on TNF-BA appear in 4 of the y/n studies to be at higher risk of postoperative infectious complications than patients not receiving such treatment. The question arises whether such patients are a *priori* at higher infectious risk than patients not requiring TNF-BA.

There are a number of stumbling blocks to the clear interpretation of these studies. First and most obviously, only one of the studies is prospective. There are large differences in the percentages of infections in the studies, and this might be related to that (both Talwalkar, et al.[6] and Wendling, et al.[7] found 0%, while Arkfeld, et al.[14] reported an infection rate of 36%). Thus, the definition of infection might differ among the studies, and retrospective assessment could be difficult. Furthermore, one could argue that different lengths of time are required for a patient to be considered off treatment, depending on the TNF-BA used. For instance, Dixon, et al.[15] had a 28 day threshold. Hirano, et al.[10] stopped infliximab for 3-4 weeks and etanercept for 1-2 weeks prior to surgery. While one would agree that discontinuing etanercept for 4 weeks is an effective interruption, this would not be the case for infliximab, which is usually given every 8 weeks. In addition, it is not always the case that patients were "on drug" at the time of surgery in the y/n studies. For example, Matthews, et al.[13] discontinued treatment in the TNF group for 2 weeks before and after surgery. One would, therefore, have to conclude that the increased risk found in this study was due to other factors. Furthermore, many of the studies included only a small number of patients, making it difficult to detect differences between the groups. Finally, the type of surgery could well be of relevance to the rate of infectious complications.

The largest study included in the analysis was presented as an abstract.[15] This study included a total of 5 groups ["on" and "off" drug during 28 days presurgery, "on" and

Table 1. Summary of the Results of All Included Studies

Study	P/R	Type	Pat. TNF-Block (n)/ Procedures (n)	Controls (n)/ Procedures (n)	Type of surgery	Disc (n)/ cont (n)	Surgical site Infection (%)‡	Conclusion
Full text								
Bibbo and Goldberg[4]	P	y/n	16/72	15/69	Foot/Ankle-surgery	n.a.	6/7	No increased risk
Giles, et al.[5]	R	y/n	35/n.d.	56	Orthopaedic	n.a.	20/5	Increased risk
Talwalkar, et al.[6]	R	c/disc	11/16	n.a.	Orthopaedic	12/4	0/0	No increased risk
Wendling, et al.[7]	R	c/disc	30/50	n.a.	Orthopaedic & Non-orthop.	18/32	0/0	No increased risk
den Broeder, et al.[2]	R	y/n	n.d./196	n.d./1023	Orthopaedic	n.a.	7/4	No increased risk
		c/disc	n.d./196	n.a.		104/92	6/9	No increased risk
Ruyssen-Witrand, et al.[8]	R	c/disc	92/127	n.a.	Mixed	n.a.	9	No increased risk*
Corrao, et al.[9]	R	y/n	26/n.d.	210/n.d.	Mixed	n.a.	0/0	No increased risk
		c/disc	26/n.d.	n.a.	Mixed	21/5	0/0	No increased risk
Hirano, et al.[10]	R	y/n	39/39	74/74	Orthopaedic	n.a.	5/7	No increased risk
Kawakami, et al.[11]	R	y/n	49/64	63/64	Orthopaedic	n.a.	13/2	Increased risk
Abstracts								
Shergy, et al.[12]	R	Cases	63/76	None	Orthopaedic	n.a.	3	No increased risk
Matthews, et al.[13]	R	y/n	30/n.d.	96/n.d.	Orthopaedic	n.a.	23/7	Increased risk
Arkfeld, et al.[14]	R	y/n	n.d./11	n.d./11	Ellbow arthropalsty	n.a.	36/9	Increased risk
Dixon, et al.[15]	R	y/n	1348/1694	155/179	Mixed	n.a.	7/7	Increased risk†
		c/disc	1348/1694	n.a.	Mixed	337/1357	6/7	Increased risk†
Kanbe, et al.[16]	R	Cases	43/43	None	Orthopaedic	n.a.	5	No increased risk

P, prospective; R, retrospective; y/n, "yes/no-studies"-comparison of patients with and without TNF-blockers; c/disc, "continued/discontinued"-studies - comparison of patients who continued or discontinued treatment with TNF-blocking agents; n.d., not determined; n.a., not applicable; TNF-BA, tumour necrosis factor blocking agents.

*c/disc is stratified in 3 groups (depending on duration of discontinuation), infections are mentioned only for the total group, the total complication rate was not influenced by time of discontinuing the drug.

†The authors of the mentioned abstract [15] conclude that there "appears" to be "a higher risk of infection". Please also see main text.

‡Infections: in c/disc studies percentages for infections are given as: "discontinued/continued". In y/n studies percentages for infections are given as: "with TNF-BA/without TNF-BA".

"off" drug at time of surgery, "DMARD" (disease-modifying anti-rheumatic drug) group]. For our presentation, the groups "on" and "off" drug at the time of surgery were analyzed. It is of relevance to note that when Dixon, et al.[15] compared the DMARD group with the group on drug, they stated that "after allowing for other risk factors" there "appears" to be an increased risk for infections in patients exposed to TNF-BA. However, the data presented also show that there is no statistically significant difference in the rate of infections between those on or off drug. The confidence interval found is wide [OR 1.07 (0.58, 1.96)]. The interpretation of these results is, therefore, somewhat difficult: given the confidence interval, the real risk may be lower in the TNF-BA group, but could also be twice as high as in the control group. However, given the data presented, an appropriate interpretation would be that the results do not nec-

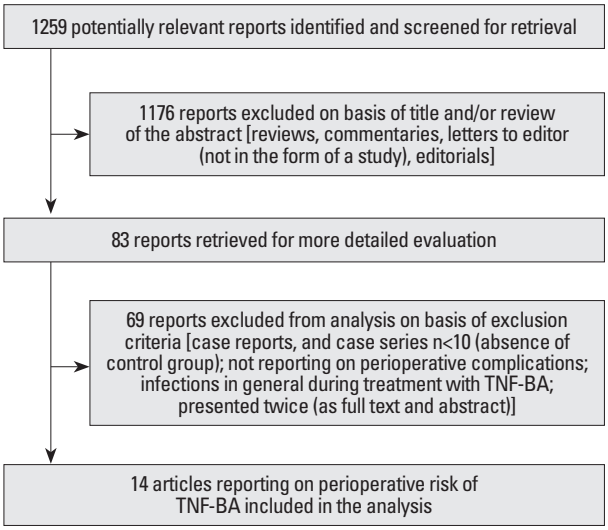

Fig. 1. Literature review flow chart. TNF-BA, tumour necrosis factor blocking agents.

essarily support the assumption of an increased infectious risk during treatment with TNF-BA.

A number of national specialist societies issued recommendations. The British Society for Rheumatology, for instance, recommends balancing the risks of postoperative infections against the risk of a peri-operative flare. If treatment is stopped, consideration should be given to stopping at a point before surgery that is 3 to 5 times the half-life of the drug (for infliximab that would be 8-9.5 days, etanercept 100 h, adalimumab 15-19 days). Treatment should not be restarted after surgery until there is "good wound healing and no evidence of infection".[17] The ACR advises that biologic agents (not restricted to TNF-BA) not be administered during the perioperative period: for at least 1 week prior to and 1 week after surgery. The "pharmacokinetic properties" of the drug used and the "type of surgery" should be taken into account.[18] The German Association of Rheumatology recommends to withhold the drug for a duration of twice the drug half-life before surgery.[19]

Given the data on TNF-BA presented in the reviewed studies, we could not find conclusive evidence that perioperatively continued treatment with TNF-BA is associated with an increased number of infectious complications, compared to discontinued treatment. This is similar to the experience with methotrexate.[20] We believe that it is important to prevent situations that make corticosteroids necessary postoperatively, as these are associated with an increased risk of infections. The data available from these studies are not sufficient to allow final recommendations. The published literature does not necessarily support an increased risk for infection. However, the available evidence does not necessarily deny an increased risk for infection when TNF-BA are continued perioperatively. Large prospective trials are needed to finally clarify the risk of infection. Until such data are available our own pragmatic approach would be to schedule surgery at the end of a medication interval and probably add one extra "safety" week prior to surgery. This approach would be supported by the fact that most patients start to flare at that time point, indicating that the effects of the drug are wearing off. Treatment should be restarted when wound closure is more or less complete. For example, when suture material has been removed. This approach is similar to that proposed by the ACR.[18]

In summary, while in theory there is an increased risk of infections when TNF-BA are administered perioperatively, the available literature does not necessarily support this. It rather appears that patients receiving TNF-BA are a priori at a higher risk of postoperative infections than are patients not receiving this treatment. However, it should be emphasized that the quality of most trials published is rather poor. Given the-limited-published evidence, we believe that a pragmatic approach, scheduling surgery at the end of the drug interval and adding one "safety" week prior to surgery is an acceptable plan in daily clinical practice.

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