

## Current Practice of Anti-TNF- $\alpha$ Treatment in Inflammatory Bowel Disease: Results From A National Survey in Sweden

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Received: July 4, 2014

Revised: August 25, 2014

Accepted: August 26, 2014

Published online: December 21, 2014

### ABSTRACT

**AIM:** To assess current practice of anti-TNF- $\alpha$  treatment in inflammatory bowel disease among Swedish gastroenterologists.

**METHODS:** A web-based questionnaire consisting of 26 multiple-choice questions was sent to 272 gastroenterologists in adult practice.

**RESULTS:** Of the 112 gastroenterologists (41%) that responded, all 102 in inflammatory bowel disease practice used anti-TNF- $\alpha$ . Almost all (97%) used combination therapy with immunomodulators and three quarters (73%) used both thiopurines and methotrexate as immunomodulators. The dominant treatment strategy was the "rapid step up" model, favored by 67%. Two thirds continued with combination therapy for more than 6 months and 80% had actively discontinued anti-TNF- $\alpha$  treatment in patients with longstanding remission. Two thirds (61%) had experience of anti-TNF- $\alpha$  during pregnancy and breast-feeding. The dominant strategy, advocated by 91%, was to continue treatment during the first two trimesters, and,

if necessary, resume after delivery. All gastroenterologists screened for tuberculosis, 88% for hepatitis B and C, but only 33% vaccinated regularly against varicella zoster and MPR.

**DISCUSSION:** Respondents from university hospitals were more likely to discontinue anti-TNF- $\alpha$  treatment (91% vs 70%,  $P=0.01$ ), use rapid infliximab infusions (24% vs 7%,  $P=0.004$ ), and use IGRA testing in tuberculosis screening (88% vs 71%,  $P=0.04$ ). They were also less likely to use single infliximab infusions as rescue therapy for ulcerative colitis (14% vs 33%,  $P=0.05$ ).

**CONCLUSIONS:** Recent advances in anti-TNF- $\alpha$  treatment of inflammatory bowel disease seem to have been adapted to a large extent by Swedish gastroenterologists. Minor differences in clinical practice were observed between university-based and other gastroenterologists.

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**Key words:** Anti-Inflammatory Agents/therapeutic use\*; Antibodies Monoclonal/therapeutic use\*; Inflammatory Bowel Diseases/drug therapy\*; Questionnaires, Physician's Practice Patterns

Hindorf U, Almer S. Current Practice of Anti-TNF- $\alpha$  Treatment in Inflammatory Bowel Disease: Results From A National Survey in Sweden. *Journal of Gastroenterology and Hepatology Research* 2014; 3(12): 1396-1400 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/970>

### INTRODUCTION

Crohn's disease and ulcerative colitis are chronic inflammatory disorders that affect more than 60,000 people in Sweden<sup>[1]</sup>. Here, anti-TNF- $\alpha$  antibodies have been used in the treatment of Crohn's disease (CD) since 1999 and in recent years also in the treatment of ulcerative colitis (UC). Anti-TNF- $\alpha$  antibodies are usually initiated as a second line treatment in patients failing classic immunosuppression (i.e. thiopurines) due to intolerance or lack of response, while primary

anti-TNF- $\alpha$  treatment mainly has been reserved for younger patients with aggressive or extensive disease.

The use of anti-TNFs for the treatment of inflammatory bowel disease (IBD) in Sweden has increased during the last few years. As a result both the profession (the Swedish Gastroenterological Association; SGA) and the authorities (the Medical Products Agency; MPA) have developed guidelines during the last years<sup>[2,3]</sup>. These guidelines, which to a large extent are based on European consensus<sup>[4,5]</sup>, have addressed treatment indications, the use of anti-TNF- $\alpha$  antibodies during pregnancy and lactation, and the risk for infections as well as recommendations regarding vaccinations prior to initiation of anti-TNF- $\alpha$  treatment. When this survey was performed, only two anti-TNF drugs, infliximab (IFX) and adalimumab (ADA), were approved for the treatment of IBD in Sweden.

The primary aim of this study was to assess current clinical practice of anti-TNF- $\alpha$  treatment in IBD and to see whether workplace (larger IBD centers, i.e. university hospitals, compared to other types of healthcare providers, i.e. smaller hospitals and private practice) or clinical experience as a gastroenterologist had an impact on treatment decisions. The secondary aim was to investigate adherence to recent guidelines.

## METHODS

This was a national cross-sectional survey consisting of 26 main questions, some of which had follow-up questions, constructed and distributed as a web-based questionnaire and sent by e-mail to gastroenterologists throughout Sweden with the effort of reaching all practicing specialists.

A list of all physicians with board certification in Gastroenterology and Hepatology was received from the National Board of Health and Welfare (Socialstyrelsen) during a previous web survey on thiopurines in inflammatory bowel disease<sup>[6]</sup>. This list was updated with current information and a total of 272 physicians received the questionnaire on two occasions, first on the 15<sup>th</sup> of January 2013 and a reminder on the 29<sup>th</sup> of January 2013. Entries were closed on the 10<sup>th</sup> of February 2013.

Statistical analyses were carried out using IBM SPSS Statistics 20 (Somers, NY). Univariate analysis was performed using the Chi-square test. All reported *P*-values were two-sided and *P*-values <0.05 were considered statistically significant.

Since the questionnaires were answered anonymously, and no specific patient related information was asked for, there was no need for an application to the ethical committee.

## RESULTS

A total of 112 gastroenterologists (41%) responded (Table 1) and

**Table 1** Response rates in the six healthcare regions.

Healthcare regions	Gastroenterologists receiving the survey (n)	Gastroenterologists responding to the survey (n)
Northern	27	6 (22%)
Southern	64	33 (52%)
Southeast	27	14 (52%)
Stockholm	81	29 (36%)
Uppsala-Örebro	40	20 (50%)
Western	33	10 (30%)
<b>Total:</b>	<b>272</b>	<b>112 (41%)</b>

of the 102 (91%) who treated IBD patients, all had experience of infliximab (IFX), 95% of adalimumab (ADA) and 23% of certolizumab. The formal decision to start anti-TNF- $\alpha$  treatment was taken at IBD conferences according to 75% of the respondents and by the individual physician according to the remaining 25%.

### Treatment strategies

Two thirds (67%) used a "Rapid step-up" strategy (position on treatment with TNF inhibitors within 6 months of diagnosis) and one third (37%) used a "top down" approach in patients with risk factors for aggressive disease. Almost all (97%) used combination therapy with TNF inhibitors and immunomodulators (IMM); 73% used both thiopurines and methotrexate, while 27% only used thiopurines. Two thirds (66%) continued with combination therapy for more than 6 months, while 11% discontinued TNF inhibitors and 9% IMM after 6 months. The greatest impact on the use of combination treatment had disease severity (91%) and previous response to IMM (80%).

Failure to respond resulted in dose escalation (91%), mostly by shorter intervals between treatments (IFX; 62%, ADA, 68%), or change of TNF inhibitor (9%). Half (51%) had experience of de-escalation (IFX;> 8v, ADA;> 2v) before planned discontinuation (86%) or due to frequent infections (31%). The majority (80%) had actively discontinued treatment with TNF inhibitors and then primarily in patients with at least 1 year of clinical remission.

In ulcerative colitis (UC), 95% used TNF inhibitors as rescue therapy in severe relapses and 94% as maintenance therapy. Only IFX was used as rescue treatment and then mostly (73%) as induction therapy with three infusions (week 0, 2 and 6). The most common reason (91%) for maintenance therapy with TNF inhibitors were active disease despite optimized IMM.

We observed that gastroenterologists working at university hospitals, compared to other institutions, were more likely to actively discontinue anti-TNF- $\alpha$  treatment, were more experienced in rapid (30 minutes) IFX infusions, and less likely to use single anti-TNF infusions as rescue therapy in UC (Table 2). Clinical experience, defined as more than 10 years as a specialist, had no impact on any treatment decisions.

**Table 2** Differences between gastroenterologists working at and outside university hospitals.

	University hospital	Other hospitals and private practice	<i>P</i> -value
Female gastroenterologists	13/51 (25%)	11/61 (18%)	0.36
Less than 10 years of clinical experience	19/51 (37%)	19/61 (37%)	0.55
Less than 75% of time devoted to clinical duty	30/51 (59%)	28/61 (46%)	0.19
Experience of IFX, ADA and CLZ	10/51 (20%)	13/51 (25%)	0.64
Use "Rapid step up"	27/41 (66%)	39/58 (67%)	1.0
Use "Top down"	15/41 (37%)	22/58 (38%)	1.0
Use both thiopurines and methotrexate in combination therapy	32/41 (78%)	34/51 (67%)	0.25
Actively discontinued anti-TNF treatment	41/45 (91%)	35/50 (70%)	0.01
Only use single infusion at rescue treatment of UC	7/49 (14%)	15/46 (33%)	0.05
Experience of fast (30 min) IFX infusions	10/42 (24%)	4/54 (7%)	0.039
Experience of anti-TNF during pregnancy and breastfeeding	24/42 (57%)	33/51 (65%)	0.52
Routinely screen for TB, hepatitis B/C and HIV	14/41 (34%)	17/50 (34%)	1.0
Use IGRA as TB screening	37/42 (88%)	36/51 (29%)	0.046
Vaccinate against VZV and MPR	12/41 (29%)	18/49 (37%)	0.51

**Pregnancy and breastfeeding**

The majority ( $n=93$ ) answered questions about pregnancy and breastfeeding, and 61% had experience with TNF inhibitors in these situations. The dominant strategy, advocated by 91%, was to continue TNF inhibitors during the first two trimesters of pregnancy, and, when necessary, to resume after delivery. Treatment with TNF inhibitors during breastfeeding was considered safe for the baby by 74%. Neither workplace (Table 2), nor time as a specialist affected physician experience in these regards.

**Infection screening and prophylaxis**

The majority ( $n=93$ ) also answered questions about infection screening and prophylaxis. Pre-treatment screening for tuberculosis (TB) with patients' history and chest X-ray were performed by all ( $n=93$ ), while 88% screened for hepatitis B and C and 34% for HIV. When screening for TB, 95% used some form of TB test (Interferon Gamma Release Assay (IGRA), 50%; Tuberculin Skin Test (TST), 16%; both IGRA and TST, 28%). It was more common that physicians at university hospitals used IGRA in the pre-treatment TB screening (88% vs 71%,  $P=0.04$ ). There was a tendency to start treatment without first checking IGRA outside university hospitals (61 vs 39%,  $P=0.07$ ). One third of the physicians regularly vaccinated sero-negative and unvaccinated patients against varicella zoster and MPR, with no difference between university and other hospitals (29 vs 37%,  $P=0.51$ ). Previous experience of primary VZV infection among treating physician did not affect their attitude towards pre-treatment vaccination (33% vs 33%,  $P=1.0$ ).

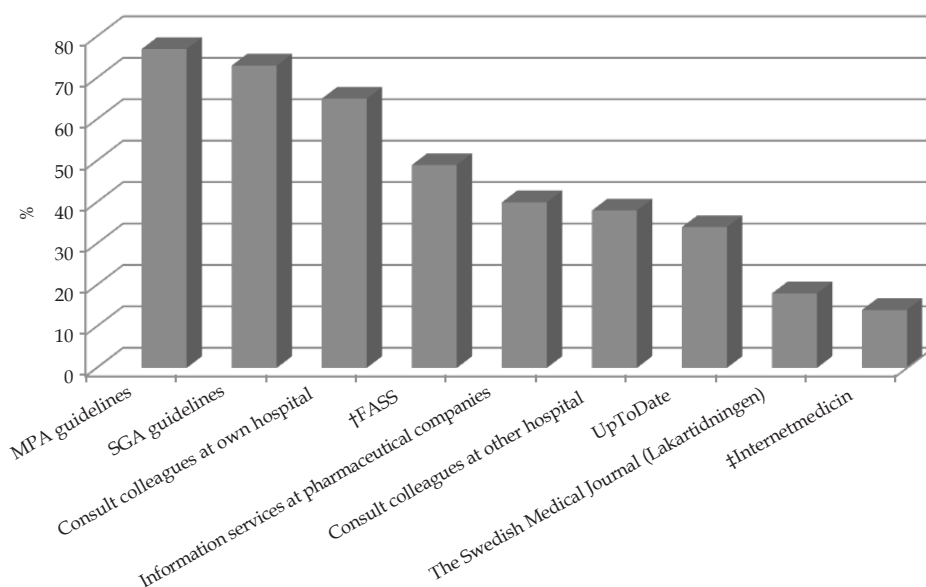
**Information sources**

According to almost all respondents results from randomized controlled studies (51%) or recommendations from experts' forums (ECCO, SGA) had most impact on their attitudes towards anti-TNF- $\alpha$  treatment of IBD. The information sources most used were guidelines by the Swedish MPA and the SGA (Figure 1). The vast majority was familiar with MPA (93%) and SGA (96%) guidelines. The only differences with regard to working place was that gastroenterologists

outside university hospitals more often consulted colleagues at other hospitals (28/49 vs 4/41,  $P<0.001$ ) and that gastroenterologists with less than 10 years of clinical experience more often consulted other colleagues at their own hospital (28/32 vs 30/58,  $P=0.006$ ). No differences regarding the use of internet sources, the attitude to randomized controlled studies or the familiarity with recent guidelines was observed.

**DISCUSSION**

This is the first survey in Sweden on treatment with TNF inhibitors in IBD, a country where the prevalence of IBD is approaching 0.7%<sup>[1]</sup>. Anti-TNF treatment in IBD is constantly evolving and it is now 5 years since the last survey regarding practice patterns of anti-TNF treatment in IBD was conducted in Europe<sup>[7]</sup>. Since then several important papers have been published on combination therapy with TNF inhibitors and IMM in CD (the SONIC study)<sup>[8]</sup> and in UC (the SUCCESS study)<sup>[9]</sup> as well as on discontinuation of TNF inhibitors (the STORI study)<sup>[10]</sup>. As this was a survey among Swedish gastroenterologists it may not reflect the practice of gastroenterologists in other countries. However, our results indicate that these studies have had impact on current practice in Sweden. This is probably, at least in part, due to their incorporation into current guidelines<sup>[2]</sup>. Thus, combination therapy with TNF inhibitors and IMM according to the "rapid step up" model<sup>[11]</sup>, dose changes according to clinical response to treatment, as well as an active attitude to therapy discontinuation in patients with longstanding clinical remission seem to have become an integral part of standard practice. Rescue therapy with IFX in severe attacks of UC quickly became popular in Sweden. This is probably due to the study by Jämerot *et al.*, which showed a significant reduction in rates of colectomy with IFX<sup>[12]</sup>. Although this study showed efficacy with a single infusion of IFX in severe attacks of UC, the practice also recommended in national guidelines<sup>[13]</sup>, the vast majority of Swedish gastroenterologists used an induction therapy with 3 infusions. This practice might be explained by the design of the ACT studies<sup>[14]</sup>, which however is conducted in a slightly different



**Figure 1** Which information sources are used when treating IBD patients with anti-TNFs? †FASS (Pharmaceutical specialities in Sweden) is the official Swedish reference on prescribed pharmaceuticals. ‡Internetmedicin is a Swedish internet knowledge base for physicians with overviews on diagnosis and treatment of medical conditions.

population with moderate to severe chronic steroid refractory UC.

In contrast to other countries where similar surveys have been performed<sup>[7,15,16]</sup>, almost all Swedish gastroenterologists (~90%) treat IBD patients with TNF inhibitors. Furthermore, in most hospitals the decision to initiate TNF inhibitors is not taken by the individual physician. Instead, these patients have to be discussed at IBD conferences, where a formal decision to start TNF inhibitors is made. There is also very few gastroenterologists in private practice in Sweden. These factors are likely to explain the similarities in practice among Swedish gastroenterologists, regardless of workplace or clinical experience.

A strength of this study is that the respondents seem to constitute a representative group of Swedish gastroenterologists with an equal distribution of participants from university and community hospitals, fairly equal response rates from the different regions and a wide distribution of specialist experience. We therefore believe that this study represents an adequate picture of how TNF inhibitors are used and monitored when treating IBD-patients, even though the response rate was 41%. We cannot, however, exclude that the respondents were more TNF inhibitor-friendly and that the results are biased towards more active treatment and monitoring.

Compared to the French study less physicians have experience of TNF inhibitors during pregnancy<sup>[7]</sup>. On the other hand, almost all who treat pregnant IBD patients with TNF inhibitors continue with treatment during the first two trimesters compared to 35% in the French study. This is most likely a reflection of the increased knowledge that has emerged in this field during the last few years as well as recent expert recommendations<sup>[17]</sup>.

Current Swedish guidelines recommend that TB is ruled out prior to anti-TNF- $\alpha$  treatment by patient history, chest X-ray and a TB test, preferably an IGRA<sup>[18]</sup>. Although all gastroenterologists screened for TB, five percent did not perform any TB test and a further 16 percent only used TST. All IBD patients that are seronegative for VZV and MPR should, according to recent Swedish guidelines, be vaccinated. Despite this, only a third of the gastroenterologists responded that this was routine clinical practice. Surprisingly, not even physicians with a personal experience of primary VZV infection among their IBD patients were more inclined to perform pre-treatment vaccination. With regard to the possible severity of primary viral infections like varicella in immunocompromised patients<sup>[19,20]</sup> as well as the substantial part of gastroenterologists not updated in current TB screening recommendations, we consider that there is a need for more continued medical education in this area.

In this survey, we also investigated how Swedish gastroenterologists seek information regarding anti-TNF- $\alpha$  treatment. Recommendations from experts' forums like ECCO and results from randomized controlled studies were most important according to the respondents. We also observed that gastroenterologists outside university hospitals were more likely to consult colleagues at other hospitals and that physicians with less clinical experience were more likely to consult colleagues at their own hospital. However, we believe that this consulting behavior between colleagues is a general phenomenon that will apply to most other aspects of patient care.

## CONCLUSION

Recent advances in anti-TNF- $\alpha$  treatment of IBD (including early use of TNF inhibitors, combination therapy with IMM and dose escalation in the lack of efficacy) seem to have been adapted to a large extent by Swedish gastroenterologists. Only minor differences in clinical practice were observed between university-based and

other gastroenterologists. Although adherence to currently published guidelines was good, we conclude that recommendations regarding infection screening and vaccination have not yet had a major impact. As in most other areas of medicine, there is a need for continued medical education. The area most in need at the moment seems to be infection-related aspects of anti-TNF- $\alpha$  treatment.

## ACKNOWLEDGMENTS

The health care company MSD has provided project resources and logistics for the implementation of the survey.

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